

Hepatitis C in people who inject drugs in the Stockholm needle exchange program

Incidence, spontaneous clearance and change in risk behaviour

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Institutet**

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HEPATITIS C IN PEOPLE WHO INJECT DRUGS IN THE STOCKHOLM NEEDLE EXCHANGE PROGRAM

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ABSTRACT

The major transmission route for hepatitis C virus (HCV) is sharing of unsterile injection equipment (needle/syringes and paraphernalia). Needle exchange programs (NEP) reduce injection risk behaviour and HCV spread among people who inject drugs (PWID). WHO has set a goal to eliminate HCV by the year 2030. To achieve this, a better understanding of the HCV spread among PWID is needed. The aims of this thesis were to study the HCV prevalence, incidence, spontaneous clearance, level of liver fibrosis and change in injection risk behaviour in PWID in the NEP in Stockholm.

In **Study I** (n=1386), we found a high 60% baseline prevalence of HCV infection in PWID and that participants became HCV infected at an early stage. Thus, 50% became anti-HCV positive within 2-5 years after start of injection drug use (IDU). Furthermore, the participants had a low awareness of their HCV status. This will have influence on injection risk behaviour and will increase the risk of HCV transmission. These findings indicate that prevention and harm reduction measures need to be implemented early on. In **Study II**, we investigated the HCV incidence among NEP participants (n=584). Overall, a high incidence rate corresponding to 22/100 person-years was noted. Factors associated with becoming HCV infected were female gender, homelessness and amphetamine use. Spontaneously clearance among those with previous exposure of HCV was significantly higher than in those who were HCV naive. High coverage of NEP, scale-up of HCV treatment and participation in effective treatment for substance use disorders, such as opioid substitution treatment (OST) need to be implemented to reduce the HCV transmission. In **Study III**, we investigated the level of HCV related liver fibrosis with liver stiffness measurement (LSM) among participants (n=203) and found that 15% had advanced fibrosis in need of early treatment and HCC surveillance. We found that an age ≥ 40 years and duration of IDU ≥ 15 years in combination with an APRI score > 1 , identified most participants with advanced fibrosis. This indicates that diagnostic work-up to detect advanced fibrosis can be simplified. In **Study IV**, we noted an overall significant reduction in injection risk behaviour of most baseline risk factors over time among participants (n=2860) in the NEP. Female gender, homelessness and amphetamine use were baseline determinants that correlated to an increased risk of sharing needle/syringes and paraphernalia, whereas OST was a protective factor.

To conclude, our studies have contributed to an increased knowledge about the prevalence and incidence of HCV infections in PWID, which highlights the need to enforce effective harm reduction interventions to prevent the spread of HCV. To eliminate HCV by the year 2030, as proposed by WHO, further implementation of NEP together with a scale-up of HCV treatment among PWID and easy access to treatment for all participants is needed.

LIST OF SCIENTIFIC PAPERS

- I. Kåberg M, Hammarberg A, Lidman C, Weiland O. **Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program.** Infect Dis. 2017 Oct;49(10):728-736
- II. Kåberg M, Navér G, Hammarberg A, Weiland O. **Incidence and spontaneous clearance of hepatitis C virus (HCV) in people who inject drugs at the Stockholm Needle Exchange - Importance for HCV elimination.** J Viral Hepat. 2018 Dec;25(12):1452-1461
- III. Kåberg M, Edgren E, Hammarberg A, Weiland O. **Hepatitis C virus (HCV) related liver fibrosis in people who inject drugs (PWID) at the Stockholm Needle Exchange - evaluated with liver elasticity.** Scand J Gastroenterol. 2019 Mar;23:1-9.
- IV. Martin Kåberg & Niklas Karlsson, Andrea Discacciati, Katarina Widgren, Ola Weiland, Anna Mia Ekström, Anders Hammarberg. **Long-term changes in injection risk behaviours among participants in a needle exchange program.** Submitted

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
AUDIT	Alcohol use disorder identification test
BBV	Blood-borne viruses
BMI	Body Mass Index
CHC	Chronic hepatitis C
CI	Confidence interval
DAA	Direct acting antiviral
DOT	Directly observed treatment
EASL	European Association for the Study of the Liver
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EOT	End of treatment
F0-F4	Fibrosis stages 1-4
FIB-4	Fibrosis-4
FPR	Fibrosis progression rate
GEE	Generalized Estimating Equation
GT	Group treatment
HAV	Hepatitis A
HBV	Hepatitis B
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HCV Ag	Hepatitis C core antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HIV	Human immunodeficiency virus
IDU	Injection drug use

INF	Interferon
IRB	Injection risk behaviour
ITG	Immediate-treatment group
ITT	Intention-to-treat
INHSU	International Network on Hepatitis in Substance Users
IR	Incidence rate
IT	Individual treatment
IVO	Inspektionen för vård och omsorg [the Health and Social Care Inspectorate]
LSM	Liver stiffness measurement
NEP	Needle exchange programs
NSP	Needle and syringe programs
OAT	Opioid agonist treatment
OR	Odds ratio
OST	Opioid substitution treatment
PEG	Pegulated
PI	Protease inhibitor
PCR	Polymerase chain reaction
PP	Per-protocol
PWID	People who inject drugs
PWUD	People who use drugs
PY	Person-years
RBV	Ribavirin
SVR	Sustained virologic response
UDS	Urine drug screen
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

1 INTRODUCTION

An estimated 71 million people worldwide are infected with hepatitis C virus (HCV) [1]. Among people who inject drugs (PWID) the prevalence of HCV is high, and the major route for HCV transmission is sharing of unsterile injection equipment (needle/syringes and other drug paraphernalia) [2, 3]. Among the 15.6 million people with recent injection drug use (IDU) worldwide, 6.1 million (39%) are estimated to be HCV infected. The global burden of disease related to previous exposure to HIV, hepatitis B (HBV), and HCV via IDU accounts for more than 10 million disability-adjusted life years (DALYs). Furthermore, it is estimated that 7 million DALYs are caused by the long-term adverse events caused by HCV [4].

Needle exchange programs (NEP), also called needle syringe programs (NSP), significantly impact both risk behaviour and HIV and HCV spread in PWID [5-8]. In 2016, the World Health Organization (WHO) presented goals for eliminating HBV and HCV by year 2030, and the scale-up of harm reduction programs [9]. Several focus-areas were proposed, including thorough investigation of the efficacy of prevention programs. Testing for blood-borne viruses (BBVs), diagnosis, linkage to care and prevention of reinfections all need to be increased to reach the elimination goal [10].

HCV treatment with direct acting antivirals (DAAs) achieve cure rates > 95% [10]. The WHO targets for HCV elimination by 2030, include a 90% reduction of new HCV cases, 80% treated HCV cases and a 65% reduction of HCV related deaths [11]. With the increased availability of DAA treatment in Europe and in the world, the feasibility of HCV elimination as proposed by the WHO will increase [12].

Previous meta-analyses have concluded that there is evidence that NEP reduce injection risk behaviour and transmission of HIV, but insufficient data concerning the effectiveness for prevention of HCV transmission [13, 14]. Other studies, however, have highlighted the effectiveness of NEP in particular when combining NEP with opioid substitution treatment (OST) to prevent HCV transmission [6, 13, 15].

In 2017, an article sanctioned by the International Network on Hepatitis in Substance Users (INHSU), highlighted research priorities needed to achieve universal access to hepatitis C prevention, management and DAA treatment in PWID. Among a total of 38 prioritised bullet points, the following were addressed [16]:

- Updated national and regional estimates of the prevalence and numbers of PWID and characteristics of these populations
- Updated national and regional estimates of the incidence, prevalence and number of people with HCV infection in PWID and opiate substitution treatment (OST) populations

- Evaluation of the implementation effectiveness, and scale-up of existing HCV-prevention interventions for PWID including OST, needle exchange programs, and treatment as prevention
- Evaluation of DAA treatment access and treatment reimbursement restrictions (e.g. fibrosis stages, drug/alcohol use and prescriber type)
- Evaluation of treatment efficacy in PWID and the long-term rate of HCV reinfections following a successful HCV treatment in PWID

The above listed priorities represent parts of the aims for this thesis. In our studies we investigated HCV prevalence, incidence, spontaneous clearance and change in injection risk behaviour in PWID over time in the NEP in Stockholm, Sweden. Furthermore, we investigated HCV related liver fibrosis and APRI score and demographic determinants, such as age and duration of IDU, to differentiate mild versus advanced fibrosis. All our data and results are discussed in the context of general HCV prevention and also in the light of the present WHO guided HCV elimination strategy.

2 HEPATITIS C

2.1 The hepatitis C virus

The hepatitis C virus is an enveloped single stranded RNA virus of the genus Hepacivirus within the Flaviviridae family. It was discovered in 1989, although its existence was observed and described already in 1975, as a ‘transfusion-associated hepatitis’ and later as non-A, non-B hepatitis [17, 18].

HCV is transmitted when HCV infected blood comes in contact with another individual’s blood stream. The major HCV transmission route in the Western world is the sharing of unsterile injection equipment among PWID [1, 3, 19]. Injection equipment include needle and syringes as well as other drug paraphernalia (cookers/filters/water). HCV may also be transmitted among people who use drugs (PWUD), who do not inject drugs, through the sharing of snorting and smoking paraphernalia (e.g. snort tubes and crack pipes) [20-22], although some studies have not found this association [23, 24]. HCV may contain infectivity days to weeks outside the body, which adds to the risk of transmission [25, 26].

Historically, and still present in some low resource settings, HCV may have an iatrogenic spread due to poor hygienic practices and the lack of testing for HCV in conjunction with blood transfusion, blood products, invasive procedures and vaccinations [27, 28]. This may also include tattooing and piercing practices [29, 30].

Sexually transmitted HCV among heterosexual partners is rare [31-33]. However, among men who have sex with men (MSM), the HCV transmission risk is increased through high-risk traumatic sexual practices and also through mucosally administered recreational drugs and sexualized drug use, also called ‘chemsex’ [34, 35].

The risk of perinatal (mother to child) transmission of HCV is around 4-5% [36, 37].

2.2 Natural history

HCV infects the liver cells and cause a chronic HCV infection in about 60-80% of cases. Conversely, 20-40% spontaneously clear the infection, the majority within six months (fig. 1). A prospective HCV study noted that the median time for spontaneous clearance was 16.5 weeks, and that 34%, 67% and 83% of infected individuals cleared HCV within 3, 6 and 12 months, respectively [38]. Spontaneous clearance is associated with female gender, symptomatic acute infection and several genetic factors, including IL28B [38-42].

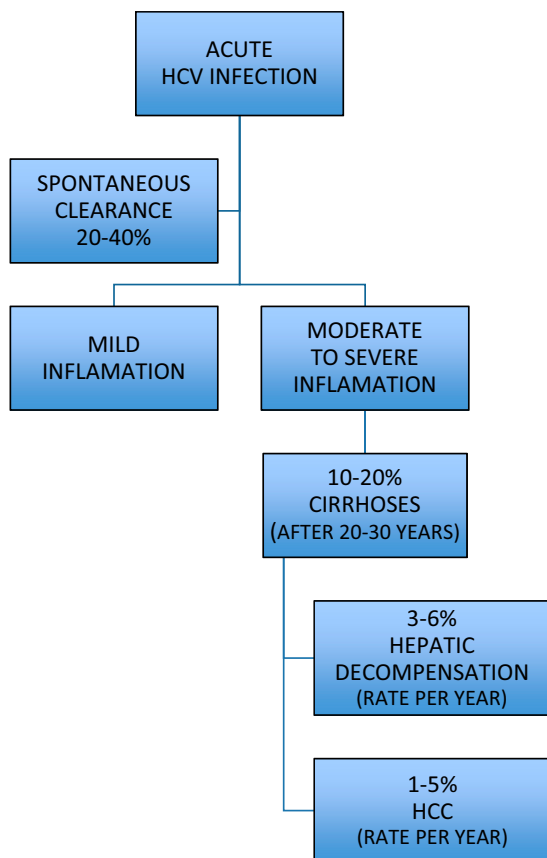


Figure 1. Natural history of HCV infection [28].

Untreated chronic HCV infection could lead to severe liver fibrosis, liver cirrhosis, decompensated liver cirrhosis, hepatocellular carcinoma (HCC) and death [43]. Development of liver fibrosis evolves slowly and gradually but may be enhanced by multiple factors (e.g. alcohol use, HIV- or HBV co-infection, diabetes mellitus, gender, age and immunosuppression) [28, 44]. After 20-30 years, 10-20% develop cirrhosis, and cirrhosis progression seems to be accelerated with duration of time [28]. Once cirrhosis is established, HCC develops at a rate between 1% and 5% per year [28, 45, 46].

2.3 Prevalence and genotypes

In 2015, the global prevalence of HCV infection was estimated to be 1.0% corresponding to 71 million people living with HCV [1].

2.3.1 Prevalence in Sweden

The overall prevalence of HCV in Sweden is estimated to be $< 0.5\%$ [43]. Since 1990, notification of acute and chronic HCV is mandatory to the Public Health Agency of Sweden, previously the Swedish Institute for Infectious Disease Control. Between 1990-2015, a total of 64,200 cases of HCV were reported to the Swedish National Surveillance Register [47]. Taking into account the diseased, emigrated, reported missing, successfully treated and spontaneously cleared cases, the Public Health Agency of Sweden estimated a total of 35,000 to 45,000 people living with HCV in Sweden in 2016. However, in this estimate, the number of undiagnosed HCV infections was not accounted for. The updated estimate for 2018 is 25,000-35,000 [48]. In previous Swedish estimates, the proportion of undiagnosed HCV cases was set to be around 20%, thus leaving an estimated number of 30,000 to 42,000 people living with HCV in Sweden in 2018 [49-51].

Annually, about 2,000 new HCV cases are reported in Sweden. Of these, approximately 150 are considered to be newly infected, i.e. have an acute symptomatic HCV infection. During the last ten years, a slight downward trend has been seen in the number of cases and in 2018 just over 1,600 cases were reported [52, 53].

The median age for HCV diagnosis is around 35 years, which indicates late detection of disease within the group [54]. HCV transmission in Sweden is strongly linked to IDU and accounts for about 70% of all cases. A large proportion of other cases reported with an 'unknown' or 'no information' transmission route is reported from psychiatric and dependency disorder clinics or correctional services, which may indicate an underlying drug use [53]. In 2016, the Public Health Agency of Sweden reported that the number of IDU related HCV infections has decreased in recent years. A downward trend was mainly seen among teenagers and young adults. However, the group aged 15–24 still stands for a relatively high proportion of all cases infected via IDU (20%) which indicates ongoing transmission of HCV among young people [53].

2.3.2 Genotypes and genotype distribution

HCV is classified in 7 major genotypes with a large number of underlying subtypes [55].

On a global level, the dominating genotypes are genotype 1 (44%), genotype 3 (25%) and genotype 4 (15%). Genotype 1 is more prevalent in high-income and upper-middle income countries (60%), genotype 3 in lower middle-income countries (36%) and genotype 4 in low-income countries (45%) [1]. There is a lower prevalence of genotype 1b and higher prevalence of genotype 1a and 3 in PWID globally, compared to the general population [56]. In Sweden, genotype 1 and genotype 3 accounts for around 50% and 30% of cases, respectively and the corresponding figure among Swedish PWID is 36-54% and 33-40% [49, 57-59].

2.4 Diagnosis and treatment

HCV is diagnosed through virological testing. Serology detects specific antibodies to HCV (anti-HCV) which are present life-long after infection, provides no immunity and indicates exposure to HCV (but not per se a viremic infection). Seroconversion appears on an average 6-8 weeks after exposure [60]. Another serological method to diagnose HCV is detection of HCV core antigen (HCV Ag) where a positive test confirms a viremic HCV infection.

The gold standard for diagnosing a viremic HCV infection is detection of HCV RNA through PCR. HCV RNA is detectable as early as 1 week after exposure and at least 4-6 weeks before seroconversion [60]. As HCV may be spontaneously cleared, two consecutive positive HCV RNA tests (with 6 months in between) normally define a chronic HCV infection. The absence of HCV RNA at end of treatment (EOT) defines treatment effect and outcome and a negative HCV RNA test twelve weeks after EOT defines a successful HCV treatment and cure, called sustained virologic response (SVR).

2.4.1 Evolution of fibrosis evaluation

Evaluation of HCV related fibrosis pre-treatment is of great importance since it defines the level of fibrosis and thus defines the level of further pre- and post-treatment investigations and follow-ups needed. Fibrosis stages may be classified in different ways but most often relate to fibrosis stages F0-F4, where F0-F1 represent absent or mild fibrosis, F2 significant fibrosis, F3 severe fibrosis and F4 cirrhosis. In settings where universal access to HCV treatment still is restricted by level of fibrosis, evaluation of fibrosis pre-treatment may be a prerequisite to meet levels of defined treatment indications (e.g. fibrosis stage \geq F2) [12, 61, 62].

The gold standard of fibrosis evaluation is liver biopsy but given the definition of gold standard, as the 'best available method under reasonable conditions' [63], the noninvasive diagnostic methods of liver stiffness measurement (LSM) has challenged this. However, LSM is not necessarily easily available in all settings.

2.4.2 Liver stiffness measurement (LSM)

LSM is performed with transient elastography, a non-invasive assessment of liver fibrosis [64, 65]. The method mostly used in Sweden is by FibroScan® and the result is obtained in kilo Pascal (kPa) where measured values are correlated to the stage of liver fibrosis (Metavir F0-F4) [66]. Liver stiffness cut-offs, used in the Swedish HCV treatment guidelines, are < 7 kPa for Metavir F0-F1, 7-9.4 kPa for Metavir F2, 9.5-12.4 kPa for Metavir F3 and ≥ 12.5 kPa for Metavir F4 indicating cirrhosis (fig. 2) [43, 67].

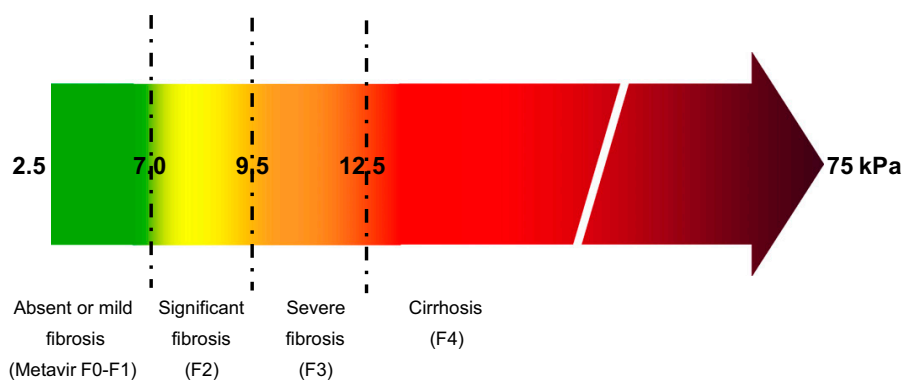


Figure 2. Cut-offs in kPa corresponding to Metavir F0-F4 for liver stiffness measurement (using FibroScan®) [67].

2.4.3 Fibrosis scores

There is a wide range of non-invasive tests to evaluate fibrosis, thus many different blood tests and algorithms have been suggested as alternatives to liver biopsy and LSM. The overall conclusion in a review was that many tests are moderately useful and more reliable when identifying clinically significant fibrosis [68]. APRI (AST to platelet ratio index) score and FIB-4 (Fibrosis-4) score, used in this thesis (paper III), were considered to have a high and moderate strength of evidence for use, respectively, in the review [68].

2.4.4 Point-of-care testing

In recent years more easily accessible tests procedures have been developed to simplify screening and diagnosis. These tests do not necessarily need advanced laboratories to diagnose HCV and testing will thus be facilitated outside hospital and health care settings. A further advantage is that testing is possible through saliva or capillary blood, without venipuncture, which is of great benefit for the PWID population due to potential difficulties in finding a usable vein for blood sampling [69, 70]. Examples of point-of-care tests are rapid tests from saliva or blood (on-site anti-HCV and/or HCV RNA test) or dried blood-spot (anti-HCV and HCV RNA test, which still need further laboratory diagnostics) [71, 72].

2.4.5 Evolution of HCV treatment

Since the first introduction of HCV treatment, the cure rates have increased dramatically from around 6-7% in the early 1990s to an almost 100% cure rate since 2015. In 1991 alfa interferon (INF) was approved as the first HCV treatment regime.

In 1998 ribavirin (RBV) was introduced as a complement to INF-alfa. RBV is a synthetic nucleoside analogue with a broad antiviral spectrum and was initially developed to target HIV infection. Ribavirin was no success for treatment of HIV but when combined with INF, a synergistic effect increased the sustained virologic response (SVR) rates during treatment of HCV to around 34-42% and was a breakthrough in HCV treatment [73, 74]. In 2002 when a modified, pegylated (PEG) interferon was introduced, treatment was not only simplified with a long-acting INF, but SVR was also overall increased to around 39% (without RBV) and 55% (with RBV). SVR for PEG-INF and RBV is dependent on genotypes, where cure rates for genotype 1 and 4 is 50% and for genotypes 2 and 3 80% [75].

The discovery and characterization of HCV encoded proteins and their functional units (i.e. NS3 protease, NS5A and the NS5B polymerase) was groundbreaking for the development of the direct acting antivirals (DAAs) [55]. When the first generation of DAAs was introduced, with the protease inhibitors (PI) telaprevir or boceprevir added to PEG-INF/RBV in genotypes 1 and 4, SVR rates increased to around 75% [76]. However, with this treatment strategy the rates of side-effects also increased with discontinuation rates of up to 40% [28].

With the second generation DAAs, introduced since 2014, SVR rates have gradually increased to >95% in most populations [77-81]. Treatment courses have been shortened to 8-12 weeks and the level of side-effects diminished, in comparison to the PEG-INF/RBV era [82, 83].

Accessed (year)	NS5B polymerase inhibitor	NS5A inhibitor	NS3/4A protease inhibitor	Genotype coverage
2014	sofosbuvir			1-6
2014			simeprevir	1+4
2014		daclatasvir		1-4
2014	sofosbuvir	ledipasvir		1+4
2015		ombitasvir	paritaprevir/ritonavir	1+4
2015	dasabuvir			1
2016	sofosbuvir	velpatasvir		1-6
2016		elbasvir	grazoprevir	1+4
2017		pibrentasvir	glecaprevir	1-6
2017	sofosbuvir	velpatasvir	voxilaprevir	1-6

Figure 3. DAAs introduced since 2014. Current recommended/reimbursed drugs by The Swedish Association of Local Authorities and Regions, as per 2018-2019, are highlighted in grey [84].

2.4.6 Follow-up after treatment

Successful treatment, achieving SVR, is associated with a reduction in the risk for advanced fibrosis, decompensated liver cirrhosis, and HCC [85-88]. However, among those with advanced fibrosis, the risk for decompensation and HCC still remains after SVR [89, 90]. Risk factors associated with persistent advanced fibrosis and risk for HCC, are pre-treatment cirrhosis, high age, diabetes, and high BMI [91, 92]. Thus, there is a need for continuous follow-up of those with advanced fibrosis to screen for possible liver disease progression, and to address the associated life-style factors post SVR [91]. Current guidelines recommend post-treatment surveillance for HCC every 6 months [83].

Another indication for long-time follow-up after SVR, is the surveillance for possible reinfections among populations with continuous risk behaviours, mainly PWID and MSM. Here, repeated HCV testing is essential to minimise further transmission and to identify those in need of re-treatment.

3 HEPATITIS C IN PWID

3.1 Prevalence of PWID and HCV

Among the 15.6 million people with recent injection drug use worldwide, 6.1 million (39%) are estimated to be HCV infected, which corresponds to 8.5% of all HCV infections globally [93]. The global prevalence of PWID and viremic HCV prevalence among PWID, is shown in figure 4 and 5.

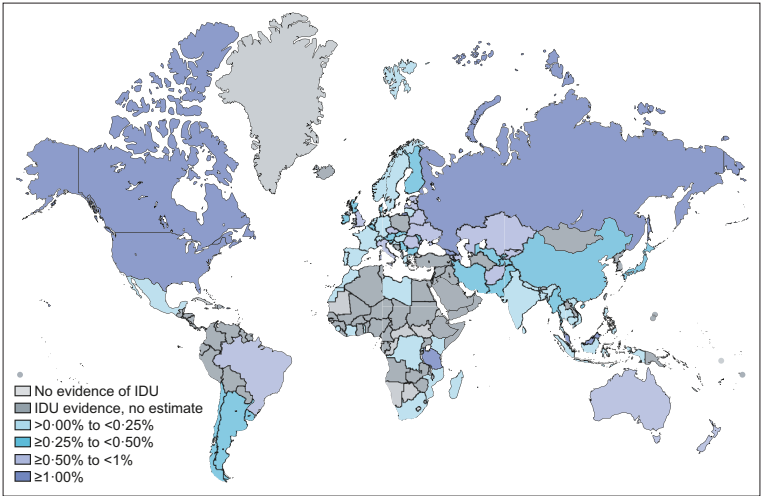


Figure 4. Global prevalence of PWID [94].

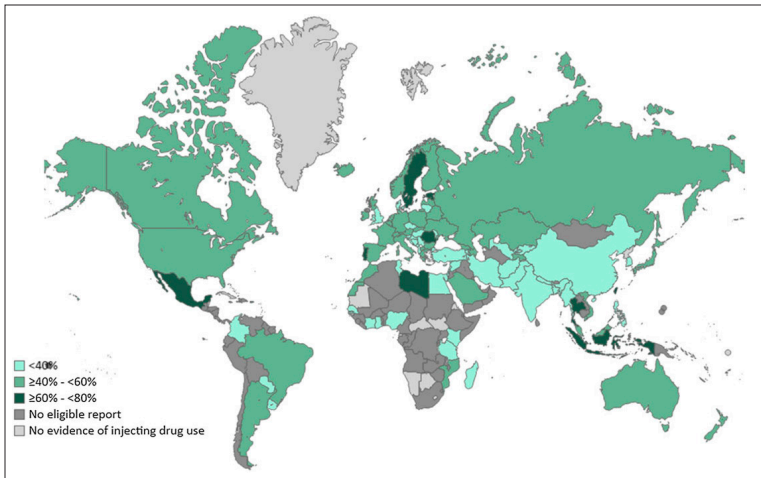


Figure 5. Global viremic HCV prevalence among PWID [93].

A global overview of HCV prevalence and sociodemographic characteristics among PWID noted that PWID in general were more exposed to high risk environments than the general population. PWID were at greater risk of police arrest, incarceration, sex work, and homelessness/unstable housing, which all are risk factors associated with increased HIV and hepatitis transmission [94].

3.2 Defining the PWID population

The definition of PWID has varied in the literature. Hence, for the evaluation of the prevalence, incidence and overall HCV treatment response among PWID, different definitions have been used. The PWID population may include those with previous injecting drug use (former PWID) and those with current injecting drug use (current PWID), most often varying from within the past 1-12 months. Sometimes even the entire OST population is defined as PWID, including those who are not currently injecting [10]. However, as shown in figure 6, there is often an overlap between these different categories, i.e. PWID in OST and current PWID.

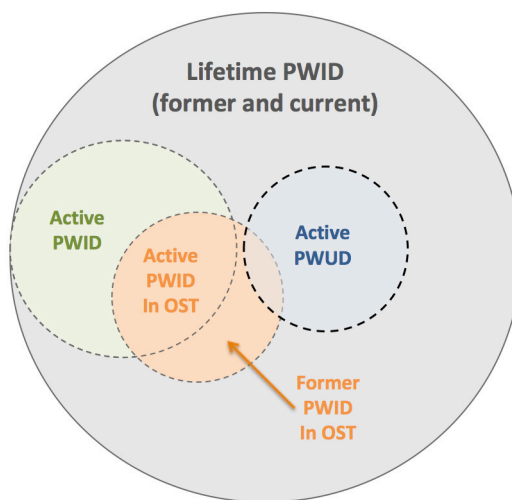


Figure 6. Defining the PWID population and the possible overlap of other populations. Figure modified from Grebely et al. [10].

There are no defined criteria used for estimation of the number of PWID in Sweden. Historically, the term “severe drug use”, indicating use of illicit drugs on a daily basis or injection drug use at any occasion during the past twelve months, has been used. Among ‘severe drug users’ it is estimated that 90% are injecting drugs [95]. In 2015, the Public Health Agency of Sweden estimated the prevalence of PWID in Sweden during 2008-2012 to a total number of 8,021 (range 6,601-10,543) [54].

This number was a dramatic decrease from the previous estimation of 26,500 PWID [95]. In 2015, a Delphi process was used to gain country expert consensus in which the number of PWID in Sweden was estimated to approximately 21,000 (Kåberg M, et al., unpublished).

3.3 Incidence of HCV in PWID

The incidence of HCV in PWID outside HCV treatment settings ranges from 5-40% per year, with a median incidence rate (IR) of 26 new infections per 100 person-years (26/100 PY) [2, 35, 96, 97]. Data from the NEP in Malmö, Sweden, investigating HCV incidence noted an incidence rate of 38/100 PY (adjusted 32/100 PY) [98]. Known factors associated with HCV infection are younger age (<20 years), younger age at IDU debut (<17 years), sharing injection equipment, history of incarceration and the combined use of heroin and amphetamine [3, 96, 98]. In a recent study from Spain the HCV incidence among new (IDU duration ≤5 years) and long-term injectors was studied [99]. An increased IR of 25/100 PY among new injectors was found indicating that that HCV infection occur early after IDU debut, confirming previous findings [57, 100, 101].

In a Canadian population-based cohort study investigating the HCV incidence between 1990-2013, a total of 5915 individuals with a prior non-viremic HCV infection (3,690 with spontaneous cleared infection and 2,225 cleared after treatment) were included. The overall proportion of reinfections was 11% (n=402) in the spontaneously cleared cohort, and 2% (n=50) in the successfully treated cohort. The overall IR was 1.3/100 PY with a follow-up time of 35,672 PY, and 1.6/100 PY and 0.5/100 PY in the spontaneously cleared and successfully treated cohort, respectively [102]. Spontaneous clearance, HIV co-infection, and IDU were significantly associated with a higher risk of HCV reinfection and OST was significantly associated with a lower risk of reinfection [102].

In the era of WHO guided HCV elimination, concerns regarding reinfections among PWID have been raised by some policy makers and clinicians [10]. With a scale-up of HCV treatment in PWID, reinfections will occur due to on-going injection risk behaviour in this population. Previous studies on reinfection rates after successful INF-based treatment range from 2-6/100 PY but so far there are only a few studies on reinfection rates after the introduction of DAA treatment [35].

3.4 Injection risk behavior among PWID in Stockholm

In 2005, in the Stockholm pre-NEP era, Nordén et al. investigated injection risk behaviour among PWID [103]. Among the participants (n=46), 62% reported injection risk behaviour during the past year. No association between baseline

determinants (e.g. gender, living situation and injected drug) and sharing of needle/syringes or paraphernalia was found, possibly explained by a low number of participants. In a study from 2009 (n=213), 71% of PWID participants reported sharing of needle/syringes the past six months and also a significantly increased level of concomitant sharing of paraphernalia [104].

In 2007-2008, a study was performed with the aim to investigate injection risk behaviour in active PWID in Stockholm (n=720). Among the participants, overall 79% reported continuous risk behaviour of receptive sharing of needle/syringes, with women reporting a significantly higher risk behaviour compared to men [105, 106].

Self-reported sharing, and re-use of injection equipment among PWID in Stockholm, were also investigated in a pilot study in 2007, (n=30) [107]. The study concluded that injection equipment often was re-used and had a long turn-over time. Overall, the syringes had been used >5 times among 85% and >15 times among 46% of the participants. The corresponding figures for re-use of needles, with a shorter 'life span', were 72% and 20%, respectively. Furthermore, all participants reported having shared needle/syringes or other paraphernalia at some time-point.

Among 2,150 remand prisoners in Stockholm, interviewed between 2002-2012, 66% reported having shared drug solution the past year and 62% and 56% acknowledged that they had received or lent out previously used needle/syringes, respectively. Factors associated with increased risk behaviour were female gender, homelessness and amphetamine use [108].

3.5 Awareness of HCV

An important factor for effective harm reduction among PWID is the awareness concerning whether you are infected and may transmit HCV or not. Awareness of HCV status is also essential for addressing HCV, enhancing the HCV care cascade and a prerequisite for HCV treatment. In Europe, the proportion of undiagnosed HCV infections in PWID range from 24% to 76% with a median of 49% [2].

The awareness of HCV status in Swedish PWID is not well studied, although one study from Stockholm has noted inadequate HCV awareness [104]. Other international studies have also concluded that the concordance between the self-reported and actual anti-HCV status in PWID is poor [109-118]. So far, most studies have examined awareness of anti-HCV status but not necessarily if a viremic and transmittable infection is at hand. However, one study utilizing HCV RNA testing found an 80% concordance between self-reported HCV positive status and a positive HCV RNA test [113].

Table 1. Studies investigating concordance between self-reported HCV status and HCV blood status among PWID.

Study	Country	Participants	Concordance with self-reported HCV status				
			anti-HCV-	anti-HCV+	Anti-HCV+/HCV RNA+	Anti-HCV+/HCV RNA-	Unknown (but post-test anti-HCV+)
		n	n (%)	n (%)	n (%)	n (%)	n (%)
Best D, et al 1999 [118]	UK	90	11/11 (100)	59/71 (83)	-	-	6/8 (75)
Stein MD, et al 2001 [117]	USA	211	15/45 (33)	102/104 (98)	-	-	51/62 (82)
Kwiatkowski CF, et al, 2002 [109]	USA	197	-	-	-	-	97/158 (61)
Schlichting EG, et al 2003 [110]	USA	653	259/484 (54)	69/74 (93)	-	-	-
Hagan H, et al 2006 [111]	USA	3004	1062/1476 (72)	288/305 (94)	-	-	331/1223 (27)
Day CA, et al 2008 [112]	Australia	208	20/37 (54)	142/146 (97)	-	-	8/13 (62)
Nordén L, et al 2009 [104]	Sweden	212	13/16 (81)	131/134 (98)	-	-	33/62 (53)
O'Keefe D, et al 2013 [113]	Australia	352	-	-	123/152 (81)	97/122 (80)*	19/23 (83)
Alanko Blomé M, et al, 2016 [116]	Sweden	229	96%**	69%**	-	-	-
Nielsen C, et al 2016 [114]	Germany	2030	339/716 (47)	-	622/857 (73)	174/457 (38)	-
Iakunchykova O, et al, 2018 [115]	Ukraine	1613	-	568/1002 (57)	-	-	-

* Figures represent self-reported answers 'negative' and HCV blood status anti-HCV- and anti-HCV+/HCV-RNA-,

** denominating numbers missing

3.6 HCV related fibrosis

As previously discussed, untreated HCV may eventually progress to severe fibrosis, compensated liver cirrhosis, decompensated liver cirrhosis, hepatocellular carcinoma and death. To identify, to diagnose HCV and to initiate HCV treatment is therefore highly prioritized to prevent this development.

A review that examined HCV related liver fibrosis among PWID (21 studies) concluded that if left untreated, the risk of severe complication will develop in mid- to late adulthood. The pooled fibrosis progression rate (FPR) was 0.12 Metavir units/year and the stage-specific FPRs were F0 to F1, 0.13; F1 to F2, 0.06; F2 to F3, 0.08; and F3 to F4, 0.12 Metavir units/year. The reported pooled incidence rates of compensated cirrhosis, decompensated cirrhosis, and HCC were 6.6, 1.8 and 0.3 events per 1000 person-years, respectively. The average time to cirrhosis (F4) and F3 was 34 years and 26 years, respectively [119].

HCV related liver fibrosis was studied in a Norwegian long-term followed cohort of PWID. In autopsy material from 102 subjects, it was noted that 16% of HCV RNA positive subjects had fibrosis \geq F3, compared to only 2% among anti HCV positive/HCV RNA negative subjects. Furthermore, among PWID who had died <15 years after HCV exposure (n=18), none had fibrosis \geq F3 as compared to 35% (n=17) of those who had died >25 years after HCV exposure [120].

Another Norwegian study looked at all-cause mortality in a cohort of PWID and noted that HCV related liver mortality increased with age. The cumulative incidence of liver related mortality among men was significantly higher in those >50 years of age compared to those <50 years of age [121].

Other studies have also described increased HCV related liver morbidity in the OST population, explained by overall longer survival on OST and thus longer duration of the HCV infection [122]. In a Swedish study in OST participants, significant liver fibrosis was found in 67% of the HCV viremic participants (n=103), which was associated with alcohol intake, higher body mass index and the presence of anti-HBc antibodies [123]. Another Swedish study investigated 'liver disease' among subjects with opioid use disorder who participated in the Malmö NEP (n=1488). Liver related mortality was significantly higher among those who were ever prescribed OST, compared to those who were not, indicating longer survival and exposure to liver disease progression [124].

3.7 Liver stiffness measurement (LSM) in PWID

An Australian LSM assessment study (n=250) performed in 2015 concluded that there was a high LSM willingness and acceptability among PWID [125]. Prior to examination, 88% rated LSM as 'very acceptable', in comparison to 72% and 32% for venipuncture and liver biopsy, respectively. After LSM, 95% rated it as 'very acceptable' and the preferred method for liver fibrosis assessment (89%) compared to venipuncture (9%) and liver biopsy (2%) [125]. Participants further reported that they were 'definitely willing' to repeat an LSM in the future (91%) and to recommend LSM to their peers (93%) [125].

Young PWID generally have mild fibrosis. Hence, in a DAA treatment study in a PWID/OST population with mean age of 48 years, 59% had no or mild fibrosis (F0-F1), 27% had moderate to advanced fibrosis and only 9% had cirrhosis when liver fibrosis was examined with LSM [126].

In an Indian study, in PWID (n=1,042), the overall anti-HCV and HCV RNA prevalence was 36% and 29%, respectively. Among HCV RNA positive participants 52%, 20% and 28% had no or mild, moderate and severe fibrosis/cirrhosis, respectively. Factors associated with severe fibrosis/cirrhosis were ‘persons who were older, had a longer duration of IDU, higher BMI, higher prevalence of insulin resistance, higher prevalence of steatosis, higher HCV RNA levels and evidence of alcohol dependence’ [127].

3.8 International and National HCV treatment guidelines concerning PWID

In international guidelines from the American Association for the Study of Liver Diseases (AASLD-IDSA), the European Association for the Study of the Liver (EASL) and INSU, treatment of PWID is recommended as a prioritized task to reduce the risk of transmission [128-130]. However, in some settings in the US and Europe, DAA reimbursement restrictions are still in place for recent PWID [61, 131, 132].

In Swedish HCV treatment guidelines, on-going or recent drug use (including alcohol) was a relative contraindication for HCV treatment until 2015. In current recommendations these restrictions have been removed. In practice however, still few PWID are treated. Before 2018, HCV treatment was restricted to moderate or more advanced liver fibrosis and cirrhosis (F2-F4) [43]. At that time, the guidelines thus excluded the younger population (including many PWID) which in a majority only have mild fibrosis.

There is evidence for acceptable HCV treatment adherence and high SVR rates within the OST population and among people with a history of IDU (including current/former IDU). SVR rates are thus comparable to those seen in people who do not inject drugs [129, 133, 134]. Despite this knowledge, HCV treatment uptake in PWID has previously been very low and limited to 1-2% of the population in studies from different countries [135-137].

Treatment uptake of HCV in active PWID has so far been low in Sweden and treatment in the OST-population also limited. The overall lifetime uptake of HCV treatment among PWID on OST has been between 1-6% in Sweden, but there are yet no published data on the yearly HCV treatment uptake among OST patients [57, 59, 123]. In Norway the cumulative HCV treatment uptake in OST patients during 2004-2013 was 14%, and the annual treatment rate <3% per year [136].

3.9 DAA treatment studies in PWID

In a post-hoc analysis of OST patients in phase II/III trials, SVR rates were similar to the non-OST patients [138]. However, the high SVR rates reflect the fact that the OST patients in these trials were not actively using drugs (since that was an exclusion criteria). There is now emerging data on DAA treatment in PWID and in the OST population and a few clinical trials have been of great importance for encouraging HCV treatment in PWID since they did not exclude and even actively included participants with current (injection) drug use.

Table 2. DAA treatment of OST/PWID populations in clinical trials, population-based cohorts and reviews.

Study	Participants (n)	Population	Positive UDS (%)	EOT (%)	ITT SVR (%)	PP SVR (%)
Clinical trials						
Co-star [139]	301	OST/PWUD	>60%			
ITG					91.5	95.5*
DTG					89.5	
SIMPLIFY [126]	103	OST/PWUD	>70%	97.1	94.2	
PREVAIL** [140]	150	OST/PWUD	47%		93***	
DOT	51				98	
GROUP	48			96	93	
TAU	51				89	
Population-based cohort						
Marcías J, et al	778	non-OST/PWID			95	97
2019 [141]	177	OST			92	95
	673	PWID			89	95
Review						
Hajarizadeh B, et al, 2019 [142]	1408	PWID/non-IDU		97.5	87.7	
	2987	OST		97.4	90.7	
	670	PWID		96.9	87.4	

UDS = Urine drug screen, ITT = intention to treat, PP = per protocol, ITG = immediate-treatment group, DTG = Deferred-treatment group, *modified ITT, **treatment contained INF-based regimens in the beginning of the study period, *** n=136, DOT = directly observed treatment, GROUP = group treatment, TAU = treatment as usual

In the clinical trials, drug use was continuous during treatment and was not associated with lower rates of SVR compared to those not using drugs [126, 139, 140]. Overall there was a high adherence to treatment. However, in the PREVAIL study, adherence was significantly lower in the ‘treatment as usual’ group compared to the ‘directly observed group’ group [140]. Also, recent

stimulant injecting (amphetamines and cocaine) in the SIMPLIFY study was associated with non-adherence [143]. On the other hand, non-adherence was not associated with lower levels of SVR [140, 143].

In the population-based cohort [141], response rates were lower among PWID compared to non-drug users, and in the review study [142], older age was associated with higher SVR (OR 2.8, $p=0.006$) and lower proportions of lost to follow-up (OR 0.45, $p=0.034$) compared to younger age.

The overall lower SVR rates in these studies could be explained by individuals lost to follow-up in these populations. This has raised the question whether SVR is the best marker for cure among PWID, or rather, if cure could be synonymous with adherence and EOT, with a focus on follow-up for possible reinfections [144]. However, lost to follow-up has also been associated with more active PWID which suggests a higher risk of reinfection [145].

3.10 Reinfection post SVR

With scale-up of HCV treatment in PWID there will be reinfections among those with on-going injection risk behaviour. Previous studies on reinfection-rates after INF-based treatment range from 2-6/100 PY but there are so far only a few published studies on reinfection after DAA treatment, with a limited amount of follow-up time [35].

In a modelling study, persistent treatment rates above 80/1000 (8%) in PWID resulted in an initial increased number of reinfections that, however, decreased over time [10]. This was explained by the fact that reinfections will occur to a higher extent than previously as chronically infected, and thus non-susceptible pre-treatment, will become susceptible for HCV after treatment induced SVR. A persistent high treatment rate of $> 8\%$ will, however, curb the reinfection rate over time (fig. 7). Thus, reinfections will occur but retreatment needs to be given as a part of the HCV elimination strategy [146].

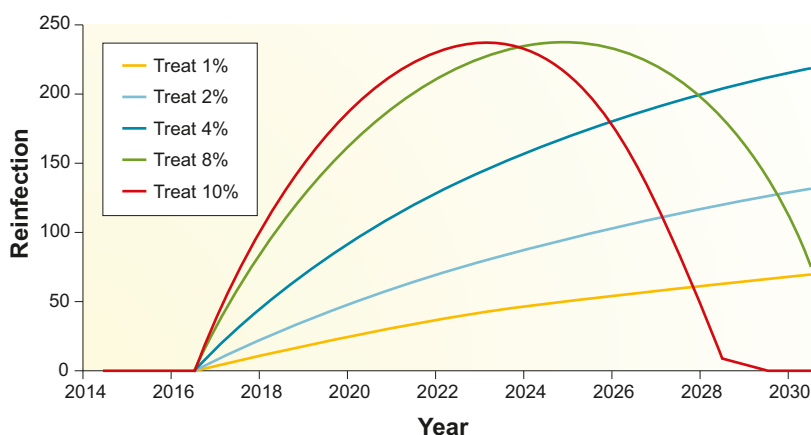


Figure 7. The concept of increased HCV reinfections post SVR among people with continuous risk behaviour due to an increased pool of HCV susceptible, and the need of a continuous high (>8%) treatment rate to curb reinfections over time. Here, visualized with Australian data from 2015 [10].

A large population-based cohort study (n=4,114) in Canada followed HCV incidence rates post SVR among former (≥ 3 years post SVR, n=1,793) and recent (<3 years post SVR, n=875) PWID treated with DAA. Overall, 40 reinfections were identified during 2,767 PY at risk with the highest IR among recent PWID (3.1/100 PY) compared to former PWID (1.4/100 PY) and non-PWID (0.3/100 PY) [147].

In a Norwegian cohort study (n=138), HCV treated (PEG-INF/RBV) participants were followed-up for reinfection and behavioural characteristics, with a 7 years median follow-up time after SVR. All reinfections were found among those with a continuous injection risk behaviour. During the follow-up, a total of 12 reinfections were found, corresponding to a reinfection proportion of 32% (12/37) and an incidence rate of 6/100 PY [148].

In a recent published study from an NSP in Scotland, participants were offered HCV treatment with PEG/RBV \pm PI [149]. Among 94 individuals who started treatment, 82% reached SVR indicating good compliance. However, at follow-up after 18 months, there were 15/77 (19.5%) reinfections in this high-risk population, with the cumulative reinfection rate of 21.5/100 PY, with a 70 person-year follow-up time. After 18 months, 9/26 (34.6%) were reinfected among those under the age of 30 years, consistent with higher rates of risk behaviour and HCV incidence rates among younger PWID [149].

The reinfection rate after SVR in OST participants in another recent multi-center study was 3.4/100 PY during the first 24-week follow-up (n=301) and 2.3/100 PY in those followed another 6-24 months after EOT (n=191). Taking into account the number of patients who spontaneously cleared the reinfection (3/10), the overall reinfection rate was only 1.6/100 PY [139, 150]. The low HCV reinfection rate post SVR in this study was possibly caused by a selection bias, since all included patients participated in OST programs which reduces the risk for reinfections per se.

3.11 The HCV care cascade

Even with universal access to HCV treatment, patients still need to be linked to care. As many studies have shown, there are many factors that might negatively affect the ‘HCV care cascade’ or the ‘retention cascade’, defined as retention in every step from diagnosis to reaching SVR [10, 151, 152]. Over time, from screening of anti-HCV, through confirmation with an HCV-RNA test, linkage to a specialist assessment, a follow-up visit for a fibrosis assessment and finally a possible treatment start - a great proportion of patient will be lost to follow-up, as shown in figure 8.

The HCV care cascade is a specific challenge in populations with concomitant co-morbidities such as on-going drug use, psychiatric co-morbidities or lack of social stability. By treating people infected with HCV geographically closer to where they already are accessing services, aiming for a ‘one-stop-shop’, the treatment retention cascade will be improved [151, 152]. Hence, HCV treatment should be offered in settings such as dependency disorder clinics, OST clinics, prisons and at NSP.

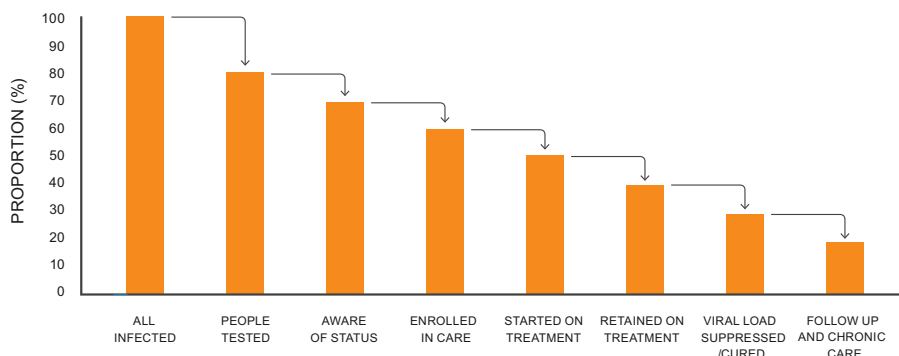


Figure 8. The concept of the ‘HCV care cascade’ among PWID [153].

4 PREVENTION OF HCV

4.1 Harm reduction

There is no universally accepted definition of harm reduction but in 2019 the organisation Harm Reduction International presented a revised definition [154]:

“Harm reduction is grounded in justice and human rights – it focuses on positive change and on working with people without judgement, coercion, discrimination, or requiring that they stop using drugs as a precondition of support”

In the article ‘How the harm reduction movement contrast itself against punitive prohibition’, by Tammi et al., harm reduction is defined through four theses on how to view drug use and people who use drugs; 1) Drug use as such should be viewed neutrally, not moralistically, 2) A person who uses drugs is a sovereign citizen and member of a community, not a deviant individual or only an object of measures, 3) Drug policy should be based on practice and science, not on ideologies and dogmatism, 4) Drug policy should respect human rights and support justice, not trample on them in the name of a ‘war on drugs’ or the goal of a drug-free society [155].

Needle syringe programs (NSP) and opioid substitution treatment (OST) are examples of harm reduction interventions. A recent global review of the access to these services noted that only 79 countries in the world have implemented these two interventions for PWID and only four countries (Australia, Austria, Netherlands and Norway) were considered as having high levels of NSP and OST [8, 156]. In the WHO strategy for HCV elimination, a goal of >300 needle/syringes distributed per PWID per year is proposed for an effective prevention of HIV and hepatitis transmission [11]. With a suboptimal needle/syringe coverage there is a risk of continuous spread of HIV and hepatitis [157-160]. So far, the global distribution coverage target for needle/syringes and OST has not been reached since only 33 needle/syringes have been distributed per PWID per year, and only 16 per 100 PWID are on OST (fig. 9) [156].

Harm reduction co-exists with other interventions such as demand reduction (e.g. primary prevention to drug use, fighting poverty, inequalities and stigma and treatment for dependency disorders) and supply reduction (e.g. destroying drug corps, interrupting drug trafficking, and targeting on drug dealing syndicates). These combined strategies are well summed-up in the ‘four pillars drug strategy’ that was first implemented in Europe in the 1990s and is based on four principals; 1) harm reduction, 2) prevention 3) treatment and 4) enforcement [161]. Lastly, there is no contradiction in the harmony between harm reduction and restrictive drug policies, as in e.g. Finland and Sweden [162].

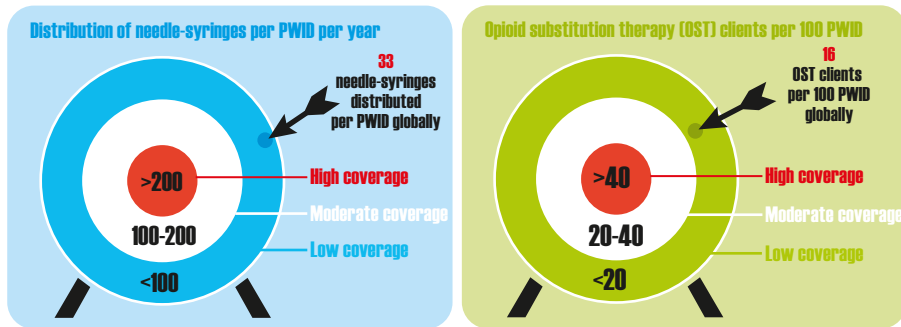


Figure 9. Global targets for the distribution of needle/syringes and opioid substitution therapy [156].

4.2 NSP/NEP

HCV and other BBVs may be transmitted through both the sharing of needle/syringes and other drug paraphernalia [163-165]. Needle syringe programs (NSP) and needle exchange programs (NEP), are recommended harm reduction interventions to reduce the spread of HIV and hepatitis among PWID [5-8]. Review-of-reviews have concluded that there is evidence for NSP in reducing injection risk behaviour and transmission of HIV but insufficient data to support the effectiveness of preventing HCV transmission [13, 14, 166]. On the other hand, there are studies indicating that NSP may prevent HCV transmission, in particular when combining NSP with OST [6, 7].

The first NEP in Sweden started in Lund in 1986, followed by Malmö in 1987. Due to political decisions, further implementation was cancelled until 2006 when a new law allowed new NEP to start up. Up until 2011, only three NEP were running in Sweden, all in Region Skåne, due to a continuous political resistance towards NEP. Between 2012 and 2015 another two NEP opened [167]. Stockholm NEP opened in 2013 and had within the first year enrolled 1,100 participants and was thus the largest NEP in Sweden.

In 2015, The Public Health Agency of Sweden published a guideline for 'health promotion and prevention work with hepatitis and HIV for PWID' [54]. The guideline recommended implementation of low threshold units targeting PWID with several interventions, including NEP. As a result, another five NEP opened between 2016-2017. In 2017, a total of 3,400 participants were enrolled in Swedish NEP and by the end of 2018, 16 out of 21 Swedish counties/regions provided NEP with a total of 21 NEP [168]. The coverage of needles and syringes per NEP participant in 2018, in Sweden, was 254 and 165, respectively (data from the InfCare NSP register).

The current Swedish NEP legislations require that participants are above the age of 18 years (previously 20 years), are registered with a personal Swedish identity number (and thus no anonymity), are considered ‘permanent residents’ in the county/region where the NEP is situated and comply with mandatory and repeated testing for HIV and hepatitis.

4.3 Change in injection risk behaviour (IRB) over time

Several studies, reviews and reviews of reviews have investigated the effect of NEP/NSP on injection risk behaviour (IRB), here defined as receptive sharing of needle/syringes or paraphernalia [13, 166]. The overall conclusion in two reviews of reviews was that there is evidence to suggest that NEP is effective in reducing IRB [13, 166]. However, due to the lack of ‘robust quality of evidence’ and presence of some biases, both reviews suggested the need for more data and future community-level studies to identify interventions needed to prevent transmission of BBVs [13, 166].

Table 3. Reviews and reviews of reviews addressing NEP/NSP effect on IRB

Study	Type	Year	Studies (n)	Conclusion
Palmateer et al. [13]	Review of reviews	2010		Sufficient data for NSP in reducing self-reported IRB.
Gibson et al.	Review	2001	23	Clear statement of evidence for NSP effect on IRB
Woodak et al.	Review	2004	28	No clear statement for NSP and IRB
Tilson et al.	Review	2007	18	Clear statement of evidence for NSP effect on IRB
Fernandes et al. [166]	Review of reviews	2017		NSP is ‘likely effective’ in reducing IRB.
Cross et al.	Meta-analysis	1998	10	NSP associated with reduced IRB
Leonard et al.	Review	1999	19	Support for NSP effect on reduced IRB
Gibson et al.	Review	2001	23	Substantial evidence for NSP effect on reduced IRB
Tilson et al.	Review	2007	18	Moderate effect of NSP on reduced IRB
Jones et al.	Review	2008	7	Conflicting statement of NSP effect on IRB
Turner et al.	Meta-analysis	2011	4	NSP associated with reduced IRB

Some studies in the reviews investigating the effect of NEP on IRB had prospective cohort designs [169-182]. However, most of the participants in these studies had a previous experience of NEP at baseline and most studies recruited street-based PWID and compared change in IRB between those with access to NEP and those without access. In conclusion, most prospective studies reported a decline in IRB at follow-up, with a greater reduction among NEP users.

Four studies (one outside of the above mentioned reviews) which investigated the prospective prevalence of IRB exclusively within a NEP, were identified. Hart et al, noted a reduction of ‘sharing’ among participants (n=76) from 15% to 11% after three to four months follow-up [174]. Vlahov et al, noted significant reductions in self-reported use of previously used syringe (22% to 11%) among participants (n=221) after a six months follow-up [181]. Vertefeuille et al, noted significant

reductions of self-reported use of previously used syringe (23% to 11%), sharing cooker (70% to 50%) and sharing cotton (59% to 39%) among HIV positive participants (n=112) after a six months follow-up [180]. Finally, Hou et al, noted a reduction of IRB (28% to 10%) among participants (n=610) that were followed annually for up to three years with the greatest risk reduction found between baseline and the first follow-up [183].

4.4 OST

OST, also called opioid agonist treatment (AOT) is the term for pharmacological treatment of severe opioid use disorder. Opioids include heroin, morphine, opium and synthetic opioids such as oxycodone, tramadol and fentanyl. OST with methadone or buprenorphine reduces opiate cravings and drug seeking behaviour through the long acting effect and elimination half-life on the opioid receptor of these drugs (compared to the short duration of effect by e.g. heroin) [184]. The pharmacological treatment is often combined with psychosocial treatment to achieve better treatment outcomes [184]. OST can also comprise pharmacological treatment of slow-release morphine or diacetyl-morphine (heroin) [185-188].

OST with methadone or buprenorphine is effective in treating opioid use disorder, protects against death by overdose and reduces the risk of transmission of blood borne viruses in particular when used in combination with NEP [189-191]. In 1966, as the second country in the world, Sweden implemented a methadone treatment program. However, due to governmental fear of over-use of methadone, only a limited number of patients were allowed to be included [192]. In 1999, with the introduction of buprenorphine, OST access was enhanced but overall access is still somewhat limited [124]. With updated Swedish guidelines in 2016, OST programs should aim to be more inclusive (with a lowered threshold for inclusion) and less excluding (decreasing involuntary discharges) [193]. The overall number of OST participants in Sweden has over the years gradually increased, with 4,468 individuals having an OST prescription in 2017 and an estimated number of over 5,000 in 2018 (personal communication Lars Håkan Nilsson) [167].

5 TREATMENT AS PREVENTION

5.1 WHO elimination goals

In May 2016, The World Health Organization (WHO) presented a strategy to eliminate hepatitis B and C as a global health threat by 2030, defined as a reduction of new infections by 90% and mortality by 65%, which would save approximately 7.1 million lives [9]. A prerequisite for achieving this goal is to reach the ‘hard to reach’ population for diagnosis, treatment and prevention of reinfection. PWID are considered a part of the ‘hard to reach’ population, also in a Swedish context, and thus need to be targeted.

5.2 Mathematical modelling

Modelling studies aim to examine the possible effects of scaled-up HCV treatment for the reduction of HCV in PWID. Other preventive measurements that could have an effect on prevalence may also be put into the model as combined interventions. Such combined interventions include high coverage of NSP and an increased access to OST, which altogether are the most effective combinations of interventions for HCV reduction [6, 191, 194, 195]. In order to model how the WHO’s goals can be achieved, several mathematical models have been developed. Although mathematical modelling may contain uncertainties in its forecasts, they give an indication of the level of intervention-inputs that may be required.

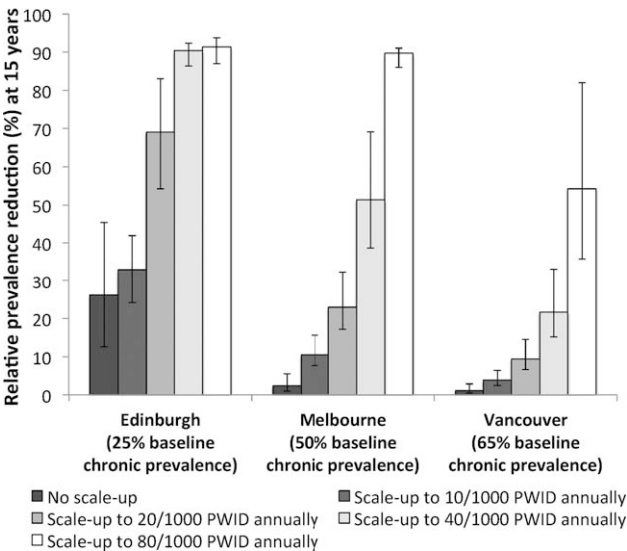


Figure 10. Modelling of HCV treatment of PWID. Baseline prevalence 25/50/65% [196].

In 2013, Martin et al published a modelling-study on HCV elimination in PWID, which gained much attention [196]. The study modelled at what rate PWID must be treated to achieve a substantial reduction in the PWID HCV prevalence over time. With a baseline prevalence of 65% and a treatment rate of 80/1000 PWID per year (8%) over 15 years, the HCV prevalence would be reduced by 50% (fig. 10). In a Swedish context, with a high HCV background prevalence of around 60%, the model projects that an increase in treatment equivalent to 8% per year over 15 years would reduce the HCV prevalence to around 30%. This corresponds to treatment of 960 PWID annually, assuming there are 12,000 chronically infected PWID in Sweden (Kåberg M, et al., unpublished).

A modelling-study from 2014 modelled the burden of HCV infection in Sweden and the impact of different DAA treatment strategies [50]. It was concluded that treating severe fibrosis (F3-F4) and doubling the annual treatment rate (to 2,260) would decrease HCC-incidence and liver-related deaths by 65–70% by 2030 but have no effect on overall prevalence and incidence. On the other hand, treating all (F0-F4) and doubling the annual treatment rate would have an effect on incidence and prevalence but less effect on liver related complications.

A European PWID modelling-study estimated the rates of HCV treatment, NSP- and OST coverage and modelled different scenarios for decrease in HCV prevalence over a 10 years period (2016-2026) [197]. For Sweden, with an HCV baseline prevalence of 60%, doubling HCV treatment would have little effect on HCV prevalence but when treating 5% of the PWID population annually, the overall prevalence would decrease to 31.3% (25.1-38.0%) within 10 years. Furthermore, if HCV treatment scale-up was combined with a scale-up of NSP and OST coverage to 80%, HCV prevalence would decrease to 9.9% (3.6-17.3%) over the 10 years period [197].

5.3 Real world data

Real world data on HCV treatment and change in prevalence is now emerging. In Australia, universal access to HCV treatment is available since March 2016, including no treatment restriction regarding active drug use. On the contrary, the PWID population is a prioritized population in the Australian National Hepatitis C Strategy [198]. An Australian study examined treatment uptake and the viremic prevalence among PWID attending NSP nationally between 2015 and 2017 [199]. Within the sample population, treatment initiation increased from 10% in 2015 to 41% in 2017 and the HCV viremic prevalence declined from 43% in 2015 to 25% in 2017.

5.3.1 HCV DAA treatment in Sweden

In Sweden, the number of treated patients has increased over time (fig. 11). During 2018 the number of treated patients tripled after reimbursement restriction for treatment were lifted. However, these data do not specifically target PWID and the number of treatments within the PWID population in Sweden is still low.

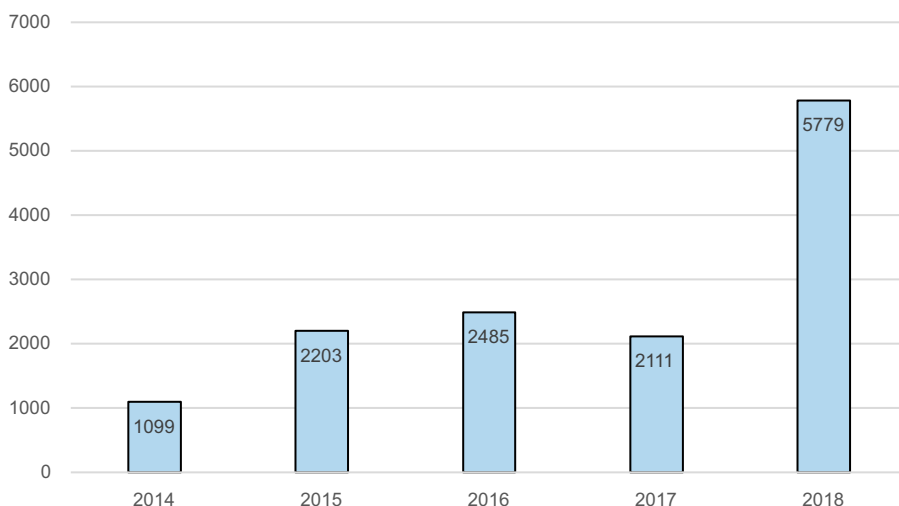


Figure 11. Number of HCV treated patients between 2014-2018. Data from the InfCare Hepatitis register.

6 AIMS

The overall aim of this thesis was to study different aspects of HCV infection among PWID at the Stockholm NEP.

6.1 Specific aims

1. To study the prevalence of HCV and pre-testing awareness of HCV status among PWID (**paper I**)
2. To study prevalence, incidence (rates), spontaneous clearance of HCV and associated baseline determinants in PWID (**paper II**)
3. To study HCV related liver fibrosis in PWID, using liver stiffness measurement (LSM), APRI and FIB-4 score, and whether mild or advanced fibrosis was found and correlate this to age and duration of IDU (**paper III**)
4. To study differences in baseline characteristics and risk behaviour depending on time-point of admission in the program (**paper IV**).
5. To study change in injection risk behaviour over time among PWID (**paper IV**)

7 MATERIAL AND METHODS

7.1 Patients, setting and study design

All studies were performed at the Stockholm NEP. The Stockholm NEP first opened in April 2013. In total 3,023 (fig. 12) were included in the Stockholm NEP during the first five years (2013-2018).

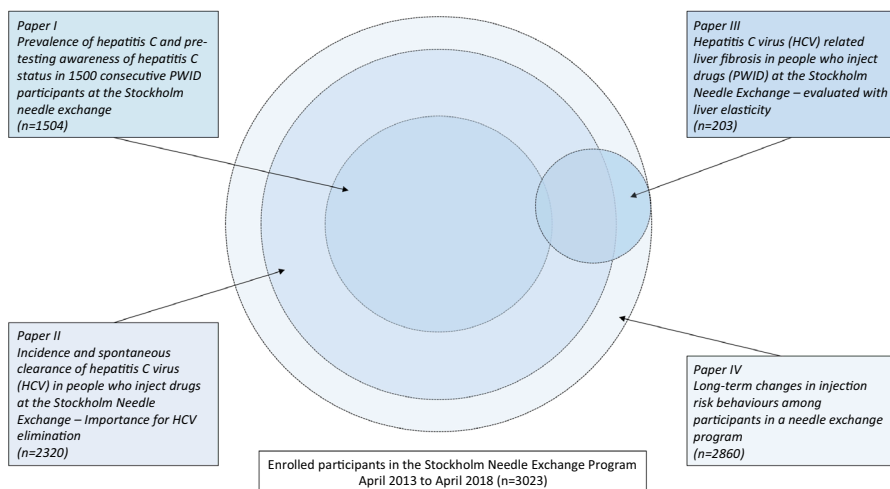


Figure 12. Overview of the study population in study I-IV.

7.1.1 The Stockholm Needle Exchange

The Stockholm NEP offers exchange of injection equipment, i.e. needle/syringe and paraphernalia, and testing for hepatitis A (HAV), HBV, HCV and HIV at inclusion is mandatory. General counselling, treatment for infectious diseases, referrals to social services and dependency disorder units including OST is provided. The NEP is organised by physicians and nurses specialised in infectious diseases and psychiatry/addiction medicine, a counsellor and midwives.

Participants were registered with their unique Swedish personal identity number, while those without were provided with a unique reserve number. At first registration, all participants participated in a face-to-face interview performed by NEP staff containing 34 questions on baseline demographics (country of birth, level of education, marital status, housing conditions and employment), past and ongoing drug use, contacts with health care services, social services, prison and prohibition services. All participants also reported their own pre-test awareness of current HIV, HBV and/or HCV status.

Risk behaviour was measured through face-to face interviews at baseline and follow-up. The following definitions of self-reported injection risk behaviour were used: 1) Having shared needle/syringe for IDU with somebody during the past month (yes or no); 2) Having shared paraphernalia with somebody during the past month (yes or no). Questionnaires and tests for HIV and hepatitis were repeated at an interval of 3-6 months.

7.1.2 Study I

In this cross-sectional study, all 1504 individuals attending the Stockholm NEP between April 8th 2013 and October 16th 2014 were consecutively included to investigate overall HCV prevalence and pre-testing awareness of HCV status. Participants were interviewed to report their own pre-test awareness of current HCV status and to report age at first IDU. Following completion of the questionnaire, venipuncture was performed for BBV tests, including HCV. We further investigated the prevalence of anti-HCV in correlation to duration of IDU to estimate the time to first HCV exposure among the NEP participants. The baseline characteristics of the included patients in the final analyses (n=1,386) are described in Table 1 of paper I.

7.1.3 Study II

In this prospective open cohort study we investigated HCV incidence, spontaneous HCV clearance, and determinants associated with new HCV infections and reinfections among the Stockholm NEP participants. All patients enrolled in the Stockholm NEP between 8th of April 2013 and 23rd of September 2016 (n=2,320) were tested for HCV at admission, and all responded to a questionnaire regarding sociodemographic data and injection risk behaviour. Follow-up tests for HCV were repeated at an interval of 3-6 months to prospectively identify new HCV infections (and reinfections) among those who were HCV susceptible (n=584). The baseline characteristics of the included patients in the final analyses are described in Table 1 of paper II.

7.1.4 Study III

In this open inclusion cross-sectional study we investigated HCV related liver fibrosis among NEP participant. Between December 8th 2016 and April 24th 2018 all patients with chronic HCV infection (CHC) infection, defined as positive HCV RNA tests > 6 months (n=964), were offered evaluation of liver fibrosis on-site, including liver stiffness measurement (LSM), a medical history and expanded blood tests to evaluate APRI and FIB-4 scores. Furthermore, the participant demographics (i.e. age, duration of IDU), history of alcohol use, diabetes mellitus and body mass index were correlated to whether mild or advanced fibrosis, as defined by LSM

(cut-off 9.5 kPa), was found. The baseline characteristics of the included patients in the final analyses (n=203) are described in Table 1 and Table II of paper III.

7.1.5 Study IV

In this prospective cohort study we investigated injection risk behaviour, receptive sharing of needle and/or syringe and paraphernalia (i.e. cookers and filters) at baseline and over a five-year follow-up (2013-2018) among the Stockholm NEP participant (n=2,860). Furthermore, we investigated demographic and drug-related determinants of risk behaviour.

Risk behaviour was measured through interviews at baseline and follow-up. The first follow-up point was set at 6 months (± 2 months) to identify possible early changes in risk behaviour following entry into the NEP. Thereafter follow-up time points were set at 12 months intervals from inclusion with a time span of ± 3 -5 months to allow for individual variation resulting in the following follow-up regimen: 12 (± 3 months), 24 (± 5 months), 36 (± 5 months) and lastly 48 (± 5 months) months. Based on previous research [108, 200, 201], eleven baseline determinants were selected for inclusion in the statistical analysis. The baseline characteristics of the included patients in the final analyses are described in Table 1 of paper IV.

7.2 Methods

7.2.1 InfCare NSP (Needle Syringe Program)

The InfCare Needle Syringe Program database (InfCare NSP) is a clinical decision tool for collecting and analysing data for participants in the Stockholm NEP (fig. 13). InfCare NSP was first introduced with the opening of the Stockholm NEP in 2013. Previously, there was no national consensus on collection and reports of data, apart from the mandatory annual report to the Swedish Board of Health and Welfare, later the Health and Social Care Inspectorate (IVO).

In 2011, the Swedish Centre for Disease Control, later The Public Health Agency of Sweden, together with representatives from the Stockholm NEP and the Region Skåne NEP, met to decide on a battery of question that would be the base for future data collection and possible research. The questions decided on were a mix of the mandatory questions for reports to IVO and validated questions from the Australian National NSP Survey Reports, the European Centre for Disease Prevention and Control (ECDC), the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the United Nations Office on Drugs and Crime (UNODC). The questions reaching consensus, were implemented into InfCare NSP and are the base for demographic data and risk behaviour data used in the studies of this thesis.

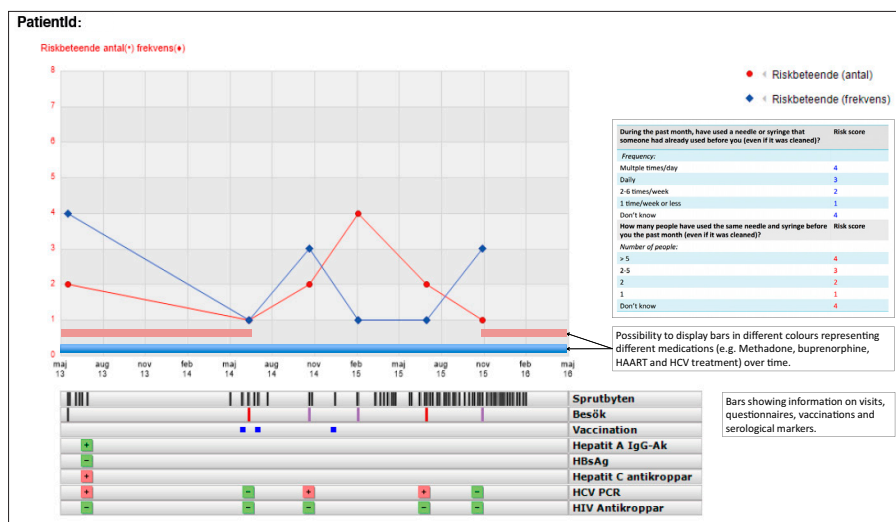


Figure 13. Graphic presentation of data in InfCare NSP. The blue and red lines depict the injection risk behaviour over time. The bars in the bottom display information on visit regularity, follow-up questionnaires (bars in black, red and purple), given vaccinations (blue squares) and serological markers (red/green +/-)

7.2.2 Immunological methods

All serological tests for HIV, HBV and HCV were performed routinely using the Abbott Architect tests (HIV Ag/ab Combo, HBsAg Qualitative II, Anti-HBc II, Anti-HBs, Anti-HCV).

7.2.3 Virological methods

HCV RNA was analysed in anti-HCV positive samples using Roche Diagnostics (Cobas TaqMan HCV Quantitative test and Cobas HCV, limit of detection 15 IU/ml).

7.2.4 Biochemical methods

All biochemical tests were performed at Karolinska University Laboratory using routine methods. A phosphatidylethanol test (B-PEth) is a specific alcohol marker in blood with high sensitivity [202, 203]. A result of $< 0.05 \mu\text{mol/l}$ represents no or low/sporadic alcohol consumption, $0.05\text{-}0.30 \mu\text{mol/l}$ a moderate alcohol consumption, and $> 0.30 \mu\text{mol/l}$ a severe/continuous consumption [204].

7.2.5 Assessment of liver fibrosis

Liver stiffness measurement

Liver stiffness measurement (LSM) was performed with transient elastography, a non-invasive assessment of liver fibrosis [64]. The result is obtained in kilo Pascal (kPa) and the value was correlated to the stage of liver fibrosis (Metavir F0-F4). Liver stiffness cut-offs in accordance with Swedish HCV treatment guidelines were < 7 kPa for Metavir F0-F1, 7-9.4 kPa for Metavir F2, 9.5-12.4 kPa for Metavir F3 and ≥ 12.5 kPa for Metavir F4 indicating cirrhosis [43, 67]. Individuals were further classified as having mild or advanced fibrosis. Mild fibrosis corresponded to LSM levels 9.4 or less and advanced to ≥ 9.5 kPa. The liver elasticity (LSM) was measured using FibroScan 402® with an M probe. Experienced members of the staff performed the LSM assessment. All participants were fasting for at least 2 hours prior to assessment. A valid assessment was defined as ≥ 10 successful readings with a success rate of > 60% and an interquartile range of < 30%.

Fibrosis scores

APRI (AST to platelet ratio index) score was calculated as: $\text{AST } (\mu\text{kat/L}) / [\text{AST (upper limit normal, } \mu\text{kat/L}) \times 100 / \text{platelet count } (10^9/\text{L})]$. An APRI score greater than 1.0 has a sensitivity of 77% and specificity of 75% for predicting F3-F4 [68].

FIB-4 (Fibrosis-4) score was calculated as: $[\text{Age (years)} \times \text{AST (U/L)}] / [\text{platelet count } (10^9/\text{L}) / \sqrt{\text{ALT}}]$. A FIB-4 score < 1.45 has a negative predictive value of 90% for advanced fibrosis and a FIB-4 > 3.25 a 97% specificity and a 65% positive predictive value to identify advanced fibrosis [205].

ALT and AST upper limit of normal was 1.1 and 0.76 $\mu\text{kat/L}$ and for men, and 0.76 and 0.61 $\mu\text{kat/L}$, respectively for women. ALT and AST in $\mu\text{kat/L}$ were normalised to U/L for the FIB-4 score, where upper normal limit for was 35 U/L for ALT and 40 U/L for AST.

7.2.6 AUDIT-C

The AUDIT-C questionnaire is a short version of AUDIT (alcohol use disorder identification test) comprising three questions about alcohol consumption patterns during the last year. The responses are summed up to a total score that varies between 0 and 12. As a cut-off score for risk use, 4 points were used for women and 5 points for men [206].

7.2.7 Statistical methods

Data from InfCare NSP were exported to and analysed in the statistical programs, JMP 10.0-13.0 ® SAS Institute Inc. or STATA 15.

All baseline demographic data were presented as proportions, mean or median levels with ranges. The Chi square test or Fisher exact two-tailed test was used to test categorical variables and the Wilcoxon rank sum test for continuous values. A p value <0.05 was considered statistically significant.

In paper II, a new HCV infection was defined as a negative HCV test (anti-HCV negative or HCV RNA negative test) at baseline followed by a later positive HCV test (anti-HCV or HCV-RNA positive). The actuarial method was used to define the time to HCV infection as the midpoint between the last HCV negative test and the following positive HCV test. All HCV susceptible subjects were followed over time to detect new HCV infections (or reinfections) or until the last follow-up test. Incidence rates (IR) were defined as number of new infections or reinfections ($n=x$) per 100 person-years ($x/100$ PY).

In paper IV, the odds of the two of risk behaviours at baseline and five follow-up points, given the 11 determinants, were modelled using Generalized Estimating Equation (GEE) regression models [207]. Given the longitudinal nature of the data, GEE regression models were used to account for the potential dependence in the risk behaviours within participants over time.

Associations between the single determinants and the odds of the risk behaviours at baseline were reported (Table 2 of paper IV) as well as relative change in odds of the risk behaviours over the five follow-up points for all determinant categories, together with a p -value testing for an overall change over time (Supplementary Table 1 of paper IV). Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All reported p -values was two-sided and p -values <0.05 was considered as statistically significant.

7.2.8 Ethics

All studies were performed in accordance to the Helsinki declaration and was approved by The Regional Ethical Review Board in Stockholm, file number; 2013/495-31/3, 2015/1374-32 (study I-IV) and 2018/904-32 (study III).

Ethical considerations

In our studies, there were no considered physical risks in answering questionnaires, undergoing LSM examination or in data retrieval. Blood sampling, which involves puncture of the skin, may be experienced as physically unpleasant. To prevent and/or reduce physical discomfort, all samplings were carried out by trained and

experienced medical staff and there were no additional blood samplings outside of general clinical work. For every eventual undesired event there was a plan for investigation, report and documentation in accordance with routines within Region Stockholm Healthcare (SLL).

No particular benefit comes from participation in study I, II and IV, beside the regular preventive activities for the individual. A needle exchange program contributes to benefits for the participants and PWID in terms of general prevention of blood borne diseases. Thus, we did not identify disadvantages of these studies for the group as a whole.

In study III, involving liver stiffness measurement with Fibroscan®, participants gained increased knowledge about their current medical situation and level of liver fibrosis and were also offered HCV treatment on-site or referral for treatment in accordance to Swedish HCV treatment guidelines. Studying HCV related liver health at the Stockholm NEP have thus contributed to benefits for the participants in the form of increased knowledge of liver health and HCV treatment that may reduce liver related morbidity and mortality.

Individuals attending the Stockholm NEP are in active drug use and may be under the influence of or intoxicated by illicit drugs. This had to be taken into account in the interaction with the participants, in the general health care provision, when performing research studies and in the interpretation of the results in this population.

8 RESULTS AND DISCUSSION

8.1 Prevalence of HCV and pre-testing awareness of HCV status (study I)

Among the participants in the final analyses (n=1,386) the anti-HCV prevalence was 82%, whereof 75% were HCV RNA positive verifying a viremic HCV infection. Hence, the prevalence of a viremic HCV infection in PWID in this Stockholm cohort was 62%. However, as more participants were enrolled in the Stockholm NEP, more participants were included in the studies which had an effect on overall HCV prevalence as depicted in table 4.

Table 4. Change in overall HCV prevalence with more included participants in study I-IV.

	Participants (n)	Year	anti-HCV prevalence (%)	HCV-RNA prevalence (%)
Study I	1386	2013-2014	82.2	62.1
Study II	2320	2013-2016	77.2	57.4
Study III	2037	2016-2018	76.1	56.9
Study IV	2860	2013-2018	73.7	55.0

The very high prevalence of anti-HCV, found among the 1,386 participants, was higher compared to many other major cities worldwide, for example Edinburgh in Scotland and Melbourne in Australia, but of the same magnitude as that reported from Vancouver, Canada [196].

Among the participants who reported a chronic HCV infection 99% were anti-HCV positive reflecting either a chronic HCV infection or a spontaneously cleared infection (Table 3 in paper I). However, 14% of those who believed that they had a chronic HCV infection were in fact HCV RNA negative (Table 4 in paper I). Furthermore, among those who believed that they never had encountered HCV 32% were anti-HCV positive and 24% HCV RNA positive. Of the 138 individuals who stated that they had spontaneously cleared their HCV infection, 32% were HCV RNA positive indicating a chronic HCV infection. Finally, of the 40 participants who reported having received treatment for HCV, with the notion that they had cleared their infection, 33 % were HCV RNA positive.

One important factor for effective harm reduction, and linkage to care, is HCV awareness among PWID on an individual level. The result of the present study showed that this awareness was lacking in large segments of PWID and that the self-reported HCV status differed from the actual status in many cases. Thus, participants who were not aware of being HCV infected carried an increased risk to transmit HCV to other PWID, and those who believed that they already were infected (but were not) had increased risk behaviour that may result in reinfections.

The participants who self-reported “not having” HCV infection had a significantly reduced injection risk behaviour compared to those reported “having” HCV. Thus, 22% of those who reported “not having” HCV reported sharing needles and syringes the past month compared to 35% of those who reported “having HCV”, ($p < 0.0001$). The corresponding figures for PWID sharing paraphernalia during the past month were 27% and 41% respectively, ($p < 0.0001$).

The overall limited HCV awareness indicates a need for repeated HCV testing with reflex testing (automatic analysis of HCV RNA among anti-HCV positive) as it is essential to diagnose and report back an accurate HCV status to better affect change in risk behaviour and for further linkage to care [208, 209].

Furthermore, we investigated the cumulated anti-HCV prevalence correlated to duration of IDU (fig. 3 in paper I). Over all, 50% had become anti-HCV positive after 4 years of IDU, women already after 2.3 years, and men after 4.9 years. The prevalence of anti-HCV in participants with IDU duration ≥ 10 years was 90%. This altogether indicate that prevention and harm reduction measures need to be implemented early on, at the very start of injection risk behaviour or if possible before injection use is started.

8.2 Change in injection risk behaviour over time among PWID (study IV)

At inclusion, 29% of the 2,860 participants in study IV had shared needle/syringe and 34% had shared paraphernalia during the past month, and one in five had engaged in both risk behaviours. The majority (60%), reported use of non-sterile equipment at last injection not necessarily representing receptive sharing, but indicating re-use of their own needle/syringe. The prevalence of HIV, viremic HCV and HBV (HBsAg positive) were 4.9%, 55% and 1.4%, respectively

At inclusion, almost half of all women had shared needle/syringe (43%) and paraphernalia (50%) during the past month compared to 25% vs. 29% for men (Table 1 in paper IV). When adjusting for confounders (Table 2 in paper IV), women were twice as likely to share needle/syringe (OR 1.95, 95% CI 1.61; 2.35) and paraphernalia (OR 2.41, 95% CI 1.99; 2.91) compared to men.

Homeless participants reported higher risk for sharing both needle/syringe and paraphernalia compared to those with stable housing (OR 1.48, 95% CI 1.20; 1.82 vs. OR 1.50, 95% CI 1.23; 1.83). At inclusion, participants ≥ 34 years of age had a 35% lower risk for sharing needle/syringe compared to their younger peers (OR 0.65, CI 95% 0.53; 0.80) (Table 2 in paper IV).

Participants injecting amphetamine were 33% and 58% more likely to share needle/syringe (OR 1.33, 95% CI 1.09; 1.61) and paraphernalia (OR 1.58, 95% CI 1.31; 1.91) respectively, compared to participants injecting heroin. Being enrolled in OST was associated with significant lower levels of sharing needle/syringe (OR 0.66, CI 95% 0.46; 0.95) and sharing paraphernalia (OR 0.35, CI 95% 0.23; 0.51).

At inclusion, HIV positive participants reported lower risk behaviour compared to HIV negative participants; needle/syringe (OR 0.56, CI 95% 0.35; 0.92) and paraphernalia (OR 0.62, CI 95% 0.40; 0.96). However, HCV positive participants reported higher levels of risk behaviour; needle/syringe (OR 1.31, CI 95% 1.10; 1.58) and paraphernalia (OR 1.41, CI 95% 1.18; 1.68) (Table 2 in paper IV).

8.2.1 Change in risk behaviour over time in the NEP

In figure 14, the change in risk behaviour in participants at different time-points following inclusion in the NEP is displayed.

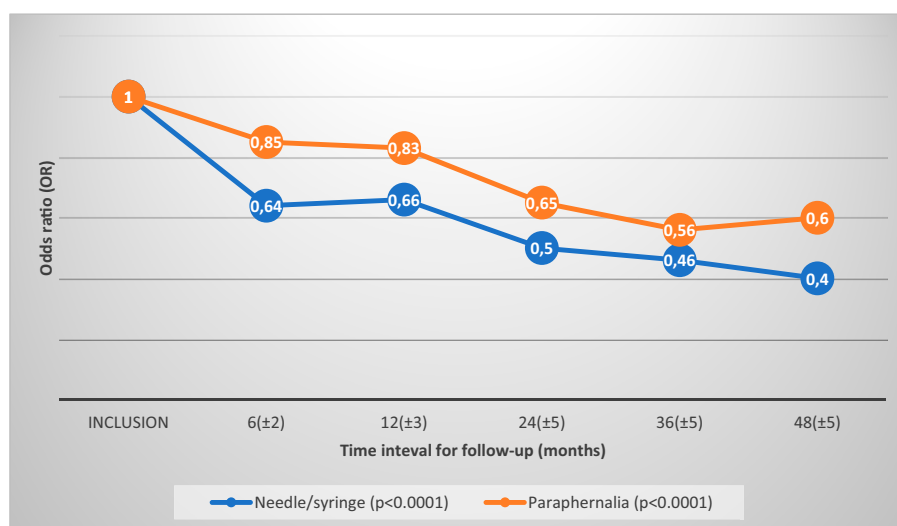


Figure 14. Change in injection risk behaviour (sharing needle/syringe and paraphernalia) following inclusion in the NEP. Odds ratio (OR) at inclusion is set at 1 as reference value. N=2860 at inclusion. P-values represent changes in risk behaviour over the whole time period.

Over all, there was a decrease in injection risk behaviour over time, both in sharing of needle/syringe and paraphernalia ($p<0.0001$ and $p<0.0001$), with reductions seen already after 6 months. There were significant decreases in risk behaviour over time by gender, living situation, heroin and amphetamine use, age at IDU debut and duration of IDU. However, those enrolled in OST, who were HIV-positive or younger (< 24 years at inclusion) did not decrease their risk behaviour (Supplementary Table 1 in paper IV).

We thus found a risk reduction in women already after 6 months regarding sharing of paraphernalia which became evident in men only after 12 months. Even though both women and men reduced risk behaviour over time, women consistently reported higher risk levels than men at each time-point (Supplementary Table 2 in paper IV). This rapid change in risk behaviour, already within the first year, is consistent with data from a longitudinal study from Baltimore, USA, where the greatest risk reduction was noticed within the first-year of follow-up [183].

8.2.2 Baseline determinants and risk behaviour by year of inclusion in the NEP

Participants enrolled in the NEP year five (of the study period) were younger, reported later IDU debut and shorter duration of IDU compared to individuals enrolled at year one. Furthermore, the prevalence of HCV declined from 61% to 42%, $p<0.001$. There were, however, no major differences in proportions of baseline injection risk behaviour for the different years of inclusion. (Table 3 in paper IV).

In summary, our findings confirmed and highlighted that women were twice as likely as men to share needle/syringe as well as paraphernalia, as found in other studies [210-212]. Furthermore, PWID with stable housing conditions reported lower levels of injection risk behaviour compared to homeless [108, 213, 214]. We also noted that an early drug and injection debut was associated with a high risk behaviour level [108, 211, 215]. Those injecting amphetamine were more likely to share injection equipment compared to those who were injecting heroin. Being enrolled in OST however, was associated with lower risk behaviour, as shown in previous reviews [5, 7, 191].

As expected, HCV-positive PWID also reported higher risk behaviour at baseline compared to those uninfected. The reverse relationship found among HIV positive participants, where an HIV positive status was associated with lower risk behaviour, may be explained by changes in risk behaviour in PWID after being diagnosed with HIV and/or possibly also by the required mandatory contact with HIV health care.

8.3 Incidence and spontaneous clearance of HCV and associated demographic factors (study II)

In study II, all HCV susceptible subjects (n=584) were followed until seroconversion or reinfection occurred, or to the time point for the last negative HCV test. The overall HCV incidence rate was 22/100 PY. The HCV incidence rate in the HCV naive (anti-HCV negative) group was 26/100 PY and in the spontaneously cleared (HCV RNA negative) group 19/100 PY. Although there were no significant differences in becoming HCV infected between the two groups (31% vs. 29%), the rate of spontaneous HCV clearance was significantly lower in the HCV naive group 20% compared to the spontaneously cleared (and thus previously HCV experienced) group 44%, ($p < 0.05$).

During follow-up in the HCV naive group, 31% became HCV infected. Baseline factors associated with HCV infection were female gender, younger age, short duration of IDU, homelessness, low education level and sharing needle/syringe the past month. In participants with a spontaneously cleared HCV infection, 29% were reinfected during follow-up. Here, baseline factors associated with reinfection were younger age, shorter duration of IDU and homelessness. Incidence rates in the spontaneously cleared cohort were in general lower than in the HCV naive group.

Despite the significant decrease in injection risk behaviour as noted in study IV, the HCV incidence rates were high and in line with previous findings in many countries [2, 35, 96-98].

Real world data on HCV incidence and reinfections rates among PWID in high prevalence settings is needed. Such data was provided in our study, with a pooled HCV incidence rate of 22/100 PY in the Stockholm PWID cohort. This may reflect the possible future levels of reinfection rates, when DAA treatment will be scaled up in Stockholm. There is however no evidence that HCV incidence outside HCV treatment and after SVR necessarily mirrors each other. On the contrary, these rates seem to diminish after SVR has been achieved [216, 217] although a recently published HCV treatment and reinfection study, in an NSP setting in Scotland, noted a reinfection rate of 21.5/100 PY [149].

A high reinfection rate post SVR poses a great challenge, and if HCV treatment per se will reduce the injecting risk behaviour or not needs to be studied further. One study indicates a reduced risk behaviour during treatment and post SVR, in spite of no significant change in daily injecting habits [216].

The high HCV incidence rate in the Stockholm PWID cohort highlights the need for interventions among NEP participants. Since the start of the NEP in 2013, 3,300 PWID have been enrolled and 1,800 unique PWID attended the program

in 2018. Data from 2018 showed that the mean needle and syringe coverage rate for NEP participants in Stockholm was 220 and 180 per person/year, respectively and thus below the recommended number in WHO guidelines of 300 needle/syringes per PWID per year, needed to reach an adequate prevention of blood borne viruses [11, 218].

The results in study II and IV further highlights the need for combined interventions, such as high coverage NEP, scale-up of HCV treatment and provision of OST, for effective HCV prevention, as concluded in previous studies [6, 13, 15]. In a recent Cochrane report, Platt et al. concluded that OST was associated with a 50% reduction in the HCV transmission rate, and that NEP alone was less effective with only a 21% reduction of the transmission rate. When stratified by region, a 56% risk reduction was found in settings with high coverage NEP in Europe. Combined OST/NEP on the other hand was associated with a 74% reduction of the HCV transmission rate [7].

8.4 Evaluation of HCV related liver fibrosis using liver stiffness measurement (LSM), APRI and FIB-4 score (study III)

A total of 203 participants were evaluated with liver stiffness measurement (LSM) which was used for fibrosis evaluation. The overall mean value was 7.2 kPa indicating that a majority had mild fibrosis. Among evaluated participants, 9% had F3 (9.5-12.4 kPa) and 6% F4 (≥ 12.5 kPa) indicating advanced fibrosis in only 15%.

Overall, a third (34%) reported having a risk consumption of alcohol during the past year by AUDIT-C. There was no significant correlation between alcohol consumption (self-reported risk consumption, $PE_{th} > 0.05$, $PE_{th} > 0.3$, or previous treatment for alcohol use disorder) and fibrosis stage (mild versus advanced). Furthermore, we found no significant association between diabetes mellitus or body mass index ≥ 30 and fibrosis stage (mild versus advanced).

However, our data may have failed to identify the risk use of alcohol over a longer duration of time. Defining long-term risk use of alcohol in our PWID population is a challenge and we might have failed to do this properly. Self-reported data on ever having treatment for alcohol use disorder may also be response biased. Furthermore, a high percentage of individuals with alcohol use disorders never seek treatment [219, 220]. It is well known that any level of alcohol consumption in combination with HCV infection, constitute a health risk [221, 222].

Only 3% had diabetes and 7% a BMI ≥ 30 , respectively. Consequently, the influence of diabetes and BMI on advanced fibrosis could not be properly evaluated.

A total of 12% participants had an APRI score > 1 . The APRI score was significantly correlated to fibrosis stages and differed in participants with mild versus advanced fibrosis ($p < 0.0001$) and in participants with or without cirrhosis ($\text{LSM} \geq 12.5$ versus $\text{LSM} \leq 12.4$). Only 9/23 (39%) of participants with APRI > 1 had advanced fibrosis ($\text{LSM} \geq 9.5$) and conversely an APRI score > 1 identified only 9/30 (30.0%) of all participants with advanced fibrosis.

We also noted an overall significant difference in FIB-4 cut-off ($1.45 <$ and > 3.25) and mild versus advanced fibrosis ($p < 0.001$). However, only 9/30 (30%) of participants with advanced fibrosis had a FIB-4 level > 3.25 . Taken together, when using an APRI score > 1 or a FIB-4 level > 3.25 as cut-offs for finding participants with advanced fibrosis ($\text{LSM} \geq 9.5$ kPa), only a limited part of those with advanced fibrosis was identified.

8.4.1 Use of age and IDU duration to detect advanced fibrosis

Of all participants, 56% were both aged ≥ 40 years and had an IDU duration ≥ 15 years. Participants aged ≥ 40 years or with an IDU duration ≥ 15 were significantly more likely to have advanced fibrosis ($p < 0.001$ and $p < 0.01$). With these respective cut-offs, 28/31 (90%) participants with advanced fibroses were identified (Table 2 in paper III).

An age of ≥ 40 years in combination with an IDU duration of ≥ 15 years identified 26/31 (84%) of participants with advanced fibrosis, however only 26/114 (23%) actually had advanced fibrosis with this cut-off. APRI > 1 was present in 13/23 (57%) of participants with an age of ≥ 40 years and an IDU duration of ≥ 15 years. When an APRI score of > 1 was combined with age ≥ 40 years in combination with an IDU duration of ≥ 15 years, all 31(100%) participants with advanced fibrosis were detected. The overlap of age of ≥ 40 years, IDU duration of ≥ 15 and APRI > 1 is displayed in a Venn diagram (fig. 15).

In summary, we found that only 15% of PWID in the Stockholm NEP had advanced fibrosis ($\text{LSM} \geq 9.5$ kPa) roughly corresponding to Metavir fibrosis stage F3 and F4. Those with advanced fibrosis are in need of immediate treatment for HCV to prevent further disease progression and also need to be included in HCC screening programs. Assessment with LSM has been well received in PWID and is reasonably effective in identifying advanced fibrosis [125, 223]. Treatment guidelines also recommend that fibrosis severity must be assessed, since it may predict future liver-related events [83, 224].

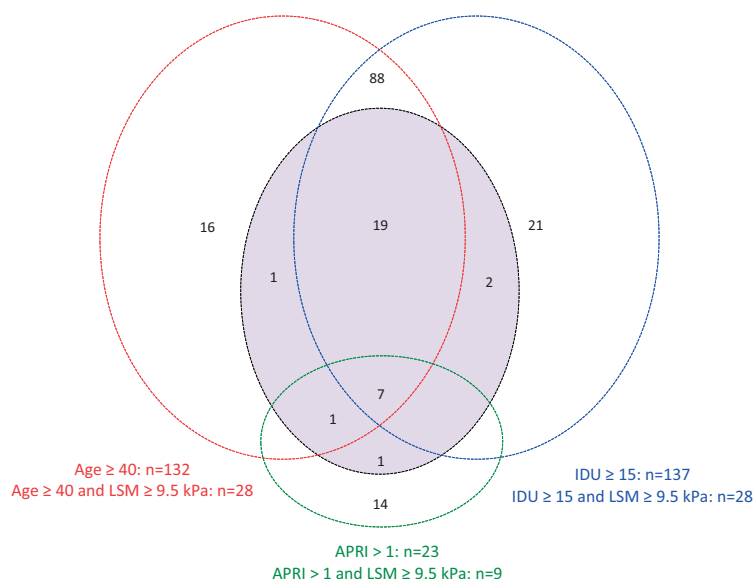


Figure 15. Venn diagram of overlap between age ≥ 40 , duration of injection drug use (IDU) ≥ 15 years, APRI score > 1 and advanced fibrosis, ≥ 9.5 kPa (filled purple circle).

With universal access to HCV treatment, without fibrosis restriction, the need for LSM evaluation has diminished. Previously, LSM was used to distinguish those eligible for HCV treatment (with fibrosis stage $\geq F2$). However, LSM evaluation to exclude or confirm severe fibrosis is still of great importance. A mandatory LSM assessment pre-treatment, however, may be a limiting factor and will thus have a negative impact on the efficacy of the HCV care cascade [10].

In our study we found that the diagnostic work-up for advanced fibrosis can be simplified with a combination of easily available factors such as age, duration of IDU and an APRI score. This allows identification of PWID in need of immediate HCV treatment to prevent further disease progression and furthermore, LSM can be avoided among PWID with mild fibrosis, identified by age < 40 years combined with IDU duration of < 15 years and APRI score < 1 . This strategy enhances the HCV care cascade where LSM is not easily available, and will thus facilitate HCV treatment initiation

8.5 Strengths and limitations

Several limitations must be considered when interpreting the results of these studies. Much of the data in all four studies (I-IV) relies on self-reported data from the participants at the Stockholm NEP. Given the nature of data collection from

face-to-face interviews, there is a risk for recall-bias as well as social desirability bias (e.g. under-reporting of risk behaviour).

Following a large cohort over time may also lead to attrition bias. We have had no opportunity to follow participants outside of the NEP and participants may have been lost to follow-up due to a variety of reasons not known to us, including voluntary termination from the NEP (e.g. choose not to come back or no longer being PWID), incarceration, geographically moving from the service and death (although the vast majorities of deaths are automatically registered in our charts).

In study II we used the actuarial method to calculate the time interval to the infection or reinfection, this might have underestimated the actual time interval. We reasoned however, that the actuarial time used, was more reasonable since the actual time for seroconversion and reinfection was unknown due to long intervals used between blood sampling.

In study I-IV we defined duration of IDU as the difference between current age and self-reported age of injection drug debut. In this estimate we have not taken into account the possibility of long periods of abstinence from IDU. Furthermore, the debut of IDU is not necessarily concurrent with being HCV exposed, although our previous data have generally demonstrated early acquisition of HCV infection [200, 201].

In study III we used LSM as the method to detect advanced fibrosis. However, LSM may be subject to confounding factors such as acute/unspecific liver inflammation, congestive heart failure, liver blood congestion after a meal, and obesity, which all are factors that can interfere and cause false high LSM levels. To minimize confounders when utilizing LSM, our participants were investigated in a fasting state, were evaluated for alcohol use and were subjected to expanded blood tests.

Lastly, in Sweden the legislation surrounding NEP requires participants to provide identification documents before admission into a NEP. Also, entry to a Swedish NEP requires an age ≥ 18 (previously 20 years) and mandatory testing for HIV and hepatitis. These procedures may have deterred some PWID from participation. On the other hand, these requirements did provide the opportunity to collect prospective clinical program data on an individual level.

9 CONCLUSION

In the four studies, performed at the Stockholm NEP between 2013-2018 we found:

- A high 60% baseline prevalence of HCV was noted at entry in the program which tended to decrease with more participants enrolled in the program, mainly explained by the enrollment of younger not yet HCV infected participants over time.
- A low awareness of the actual HCV status among PWID at enrollment was noted which will have influence on injection risk behaviour in PWID and will increase the risk of HCV transmission.
- That female gender, homelessness and amphetamine use were baseline determinants correlated to sharing needle/syringes and paraphernalia, whereas OST was a protective factor.
- That there was an overall significant reduction in injection risk behaviour of most baseline risk factors over time in the Stockholm NEP.
- That PWID in Stockholm became HCV infected relatively early. Thus 50% became anti-HCV positive within 2-5 years after debut of IDU.
- That despite a significant reduction in injection risk behaviour over time, a high HCV incidence rate was still noted both among those who were HCV naive (26/100 PY) and those who had spontaneously cleared the HCV infection (19/100 PY).
- That female gender, homelessness and amphetamine use at baseline was correlated to a new HCV infection, the same baseline determinants as noted for injection risk behaviour.
- That advanced HCV related liver fibrosis was seen in only 15% of PWID in the NEP, making them prioritized for HCV treatment and HCC surveillance.
- That a combined use of age ≥ 40 and IDU duration ≥ 15 years in combination with APRI score > 1 could be used to pinpoint PWID with advanced fibrosis.

10 SAMMANFATTNING PÅ SVENSKA

Den främsta orsaken till att hepatit C-virus sprids är att personer som injicerar droger delar icke-steril injektionsutrustning, d.v.s. nålar, sprutor och andra injektions-tillbehör (droglösning, uppdragningskärl och filter). Sprututbytesprogram bidrar till minskat injektionsriskbeteende och minskad spridning av hepatit C hos personer som injicerar droger. Världshälsoorganisationen (WHO) har satt upp ett mål att eliminera hepatit C till år 2030. För att uppnå det målet behövs ökad kunskap kring förekomst och spridning av hepatit C i den grupp som är mest utsatt för risk. Syftet med avhandlingen var därför att studera förekomst av hepatit C, frekvens av nysmitta, hur många som läker ut hepatit C, graden av leverskada orsakad av hepatit C samt hur förändring av injektionsriskbeteende ser ut över tid hos personer som injicerar droger och som är inskrivna på sprututbytet i Stockholm.

I första studien fann vi en hög (60%) förekomst av hepatit C-infektion samt att hälften (50%) blivit infekterade inom två till fem år efter injektionsdebut. Dessutom var medvetenheten begränsad kring huruvida man var infekterad av hepatit C eller inte i samband med det första besöket på sprututbytet. Dessa faktorer påverkar injektionsriskbeteendet och risken för spridning av hepatit C. Våra resultat indikerar att förebyggande åtgärder och skadereducerande insatser som sprututbyte måste tillgängliggöras i ett tidigt skede för att minska spridningen av hepatit C.

I andra studien undersökte vi förekomst av nysmitta av hepatit C bland deltagarna på sprututbytet. Sammantaget noterades en hög grad av nysmitta som motsvarade 22% per år. De som befann sig i ökad risk för att bli infekterade av hepatit C var kvinnor, hemlösa samt de som injicerade amfetamin. Personer som tidigare hade läkt ut sin hepatit C hade en större chans att göra det igen, jämfört med de som blev infekterade för första gången. Avgörande insatser för att minska spridningen av hepatit C är en kombination av 1) ökad tillgänglighet till sprututbytesverksamhet, 2) behandling av hepatit C i gruppen som injicerar droger samt 3) tillgänglig och effektiv beroendevård som t.ex. läkemedelsassisterad rehabilitering vid opioidberoende (LARO).

I tredje studien undersökte vi graden av hepatit C-relaterad leverskada hos besökare på sprututbytet med hjälp ultraljud (Fibroscan). Vi noterade att 15% hade en avancerad fibros (ärrbildning i levern) och var därmed i behov av prioriterad behandling och fortsatt uppföljning för att minska risken för ytterligare leverskada. En ålder på över 40 år och en tid längre än 15 år sedan injektionsdebut var faktorer som ökade risken för att ha avancerad fibros. Våra resultat indikerar också att yngre personer med kortare tid sedan injektionsdebut kan behandlas utan föregående ultraljudsundersökning, vilket kan underlätta utredning och öka tillgängligheten till behandling.

I fjärde studien noterade vi en signifikant minskning av injektionsriskbeteendet över tid hos deltagarna på sprututbytet. Kvinnor, hemlösa och de som injicerade amfetamin visade sig ha en ökad risk att dela nålar, sprutor och andra injektionsstillbehör, medan LARO-behandling var en skyddande faktor. Över tid har sprututbytet nått ett större antal individer som inte redan är infekterade av hepatit C i samband med första besöket, vilket skapar möjlighet att förebygga hepatit C i ett tidigare skede.

Sammanfattningsvis har våra studier bidragit till en ökad kunskap om förekomsten och graden av nysmitta av hepatit C hos personer som injicerar droger. Våra resultat har också visat att deltagande i sprututbytesverksamhet leder till ett minskat injektionsriskbeteende. Behovet av effektiva skadereducerande insatser för att förhindra spridningen av hepatit C är av stor betydelse. För att eliminera hepatit C till år 2030, som WHO föreslagit, behövs ytterligare implementering av sprututbytesverksamhet i kombination med en ökad behandling av hepatit C bland personer som injicerar droger, samt en ökad tillgänglighet till effektiv beroendebehandling som t.ex. LARO-verksamhet.

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